HPV Vaccination Uptake and Cancer Screening Practices in the Twin Cities Metropolitan Area: A Pilot Study

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Dedication

This dissertation is dedicated to my wife, Jenny, and my children, Darla, Bennett, Tate, and Lucille. You have all of my love. IWBFTE.

Abstract

Objective: Research describing the uptake and geographic variability in the human papillomavirus (HPV) vaccine is limited and has relied on data collected from large national surveillance programs. The overarching goal of this dissertation was to estimate the uptake of the HPV vaccine at the ZIP code level and to determine if uptake varied geographically.

Methods: In Manuscript 1, we recruited 1,003 men and women via a targeted Facebook advertisement campaign to complete an online survey about HPV vaccination practices. In Manuscript 2, we examined the geographic variation in HPV vaccine uptake using ZIP code level data from 760 individuals nested within 99 ZIP codes surrounding the downtown area of Minneapolis, Minnesota to identify predictors of vaccination while accounting for spatial dependence. In Manuscript 3, women aged 21-30 years were recruited online to participate in either (1) self-collected testing for HPV and an online survey, or (2) an online survey regarding their perceptions of self-collected testing for HPV infection. A variety of statistical methods were used to answer our research questions including logistic regression and proper spatial conditional autoregressive (CAR) models.

Results: In Manuscript 1, we found that receipt of ≥1 dose of HPV vaccine for women was 65.6% and 12.5% for men, which differs from previously reported Minnesota state level estimates (53.8% for young women and 20.8% for young men) and from national estimates (34.5% for women and 2.3% for men). In Manuscript 2, HPV vaccination was found to exhibit strong spatial dependence ($\hat{\rho} = 0.9966$). Accounting for spatial dependence, older age, male gender, and liberal political preference were

found to be significant predictors of HPV vaccination. In Manuscript 3, we found that self-collection was acceptable to women, and that women who self-collected a sample reported more favorable attributes of self-collection compared to women who only participated in the online survey.

Conclusions: Local estimates to assess the variation in HPV vaccine uptake are needed, as these estimates differ considerably from those obtained using survey data that is aggregated to the state or federal level. In addition, studies that examine geographic variation in HPV vaccination need to account for spatial dependence in order to identify predictors associated with vaccine receipt. Online recruitment and at home screening methods have the potential to engage women in screening by offering an approach that might be more acceptable to women of different backgrounds.

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Chapter 1. Overview of the Dissertation

1.1 Statement of the Problem

Human papillomavirus (HPV) infections in men and women present a tremendous public health burden. Effective prevention and screening strategies (i.e. vaccination against HPV, HPV testing and Pap test-based screening) are available to reduce HPV-associated disease morbidity and mortality. However, HPV vaccination has not been accepted as quickly as was originally anticipated, with significant variation at both the state and local level. Moreover, vaccination and screening are less likely to be used by at-risk populations (e.g. people living in poverty, racial minorities, or immigrants). Importantly, these are the populations that may benefit the most from HPV vaccination and cancer screening since they are at the highest risk for HPV-associated disease. As a result, health disparities continue to exist and adversely affect certain groups of men and women.

The CDC currently monitors HPV vaccine coverage and cervical cancer screening practices by piecing together results from five national health surveys that vary greatly in terms of their sampling procedures, their intended target populations, the type of data that is collected, and the expected uses of the collected information. Importantly, sampling in these surveys is such that variations at a local level (i.e. between counties or zip codes) cannot be adequately assessed. Additionally, these surveys have also been directed towards girls and have not inquired about the HPV vaccination practices of boys. These data are needed, as an ongoing concern is that if women who do not participate in screening are also those who are less likely to be vaccinated, disparities will continue to

occur and potentially grow. Research is needed in order to determine whether women who are vaccinated are also being screened, and vice versa.

The current scarcity of data at local levels also limits researchers' ability to study the associations and patterns of HPV vaccination among youth. The only method that is currently available for assessing HPV vaccination uptake involves the patchwork of surveillance systems mentioned above which lack geographic resolution. Thus, it is not currently possible to identify detailed HPV vaccination patterns and their relationship to incident infections to estimate the long-term health effects of vaccination efforts.

1.2 Specific Aims

This research aims to identify ZIP codes within the Twin Cities Metropolitan Area where screening and vaccination participation varies. The goals of this dissertation research were to obtain information regarding cancer screening and HPV vaccination from men and women at the local level, to evaluate the associations of these behaviors by place of residence, and to determine the feasibility of recruiting participants online to participate in self-collected HPV testing. In particular, the following research questions and aims were addressed:

1) Will men and women participate in online research regarding HPV vaccination and cancer screening practices?

Aim 1: Demonstrate the feasibility and cost-effectiveness of recruiting men and women for health research through the Internet.

2) Does the prevalence of HPV vaccination among men and women at a local level differ from state and national level estimates?

Aim 2: Estimate the prevalence of HPV vaccination among men and women in the Twin Cities Metropolitan Area.

3) Does the pattern of HPV vaccination uptake differ after accounting for spatial dependence?

Aim 3: Describe and evaluate the distribution of HPV vaccination uptake by ZIP code in the Twin Cities Metropolitan Area.

4) Will women participate in self-collected HPV testing after being recruited on the Internet?

Aim 4: Obtain self-collected vaginal samples for HPV testing from women recruited on the Internet to determine the feasibility of self-collected screening in this population and to determine the potential for providing underserved women with cancer screening via Internet recruitment.

1.3 Organization of the Dissertation

This dissertation consists of three inter-related manuscripts. A detailed background of the disease burden and epidemiology of HPV will be discussed, followed by the three manuscripts which will be submitted for publication. Below, the research questions and specific aims for each manuscript are presented.

Manuscript 1

Manuscript 1 investigated the potential of using an online survey to obtain HPV vaccination and cancer screening information from men and women in the greater Twin Cities Metropolitan Area. To this end, the Survey of Minnesotans About Screening and

Health (SMASH) study was developed. The primary research questions and specific aims were:

1) Will men and women participate in online research regarding HPV vaccination and cancer screening practices?

Aim 1: Demonstrate the feasibility and cost-effectiveness of recruiting men and women for health research through the Internet.

2) Does the prevalence of HPV vaccination among men and women at a local level differ from state and national level estimates?

Aim 2: Estimate the prevalence of HPV vaccination among men and women in the Twin Cities Metropolitan Area.

Manuscript 2

Manuscript 2 examined the pattern of HPV vaccine uptake at the ZIP code level for 760 men and women residing within a 25-mile radius of downtown Minneapolis, Minnesota. The primary research question and specific aim was:

3) Does the pattern of HPV vaccination uptake differ after accounting for spatial dependence?

Aim 3: Describe and evaluate the distribution of HPV vaccination uptake by ZIP code in the Twin Cities Metropolitan Area.

Manuscript 3

Manuscript 3 builds on the results of manuscripts 1 and 2. A subset of the women who participated in the SMASH study were invited to either self-collect a vaginal sample for HPV DNA testing or to respond to an online survey regarding their perceived

acceptability of self-collected screening for HPV. Specifically, the primary research question and specific aim of this manuscript was:

4) Will women participate in self-collected HPV testing after being recruited on the Internet?

Aim 4: Obtain self-collected vaginal samples for HPV testing from women recruited on the Internet to determine the feasibility of self-collected screening in this population and to determine the potential for providing underserved women with cancer screening via Internet recruitment.

This dissertation demonstrates the efficiency and feasibility of using the Internet to collect public health data and to recruit participants for interventions. This dissertation is the first study to examine the spatial pattern of HPV vaccine uptake at the ZIP code level, and to recruit women via the Internet to participate in self-collected HPV DNA testing. This dissertation suggests that specific locations can (and should) be identified in order to maximize future intervention and vaccination strategies designed to reduce HPV-associated disease. In addition, this dissertation suggests that online recruitment and screening approaches may be used to facilitate targeted screening among high-risk sub-populations, including under-screened and underprivileged women, to reduce the burden of HPV disease.

Chapter 2. Background and Epidemiology of HPV

2.1 General Background

Human papillomavirus (HPV) is the most common sexually transmitted infection in the U.S. [1], and is the necessary cause of cervical cancer and genital warts [2]. There is increasing evidence that other cancers are also associated with HPV infection (e.g. anogenital and oropharyngeal cancers) [3-4]. In total, it is estimated that 5.2% of cancers in men and women worldwide are attributable to HPV [5].

It is known that HPV infections among men and women present a tremendous public health burden; however, there remain major gaps in our understanding of how many HPV infections occur, and to what extent they will progress into serious diseases. Although screening is highly effective in reducing the incidence of cervical cancer, participation continues to vary between ethnic and socioeconomic groups [6]. More than 60% of cervical cancer cases in the U.S. occur in medically underserved and underscreened populations [7]. Additionally, HPV-associated cervical cancer rates appear to follow a unique pattern across the United States, with lower observed rates in the Pacific Northwest, Upper Midwest, and small Northeastern states, and significantly higher cervical cancer rates in the South and Central Eastern states (see Figure 2.1) [8]. In prior research conducted as part of my Master's thesis, I showed that cervical cancer rates also vary considerably within the state of Minnesota by county (refer to Figure 2.2) [9].

The FDA has licensed two HPV vaccines (quadrivalent Gardasil® in 2006 and bivalent Cervarix® in 2009) that protect against HPV types 16 and 18, the most common oncogenic HPV types [10-11]. The Advisory Committee on Immunization Practices

(ACIP) recommends using either vaccine for routine vaccination of boys and girls aged 11 or 12 years old, with catch-up vaccination recommended for those aged 13 to 26 years [12-14]. Although these vaccines have been shown to be safe and effective, uptake has been far lower than expected [15]. As of 2012, in the United States approximately 53.8% (95% CI, 51.9% to 55.7%) of girls aged 13 to 17 in the United States had received at least 1 dose of HPV vaccine (either the quadrivalent or bivalent vaccine). Of those girls who had at least one HPV dose, only 66.7% (95% CI, 64.1% to 69.3%) had received the complete three-dose regimen [15].

Uptake within the state of Minnesota is similar to that reported nationally with 55.5% (95% CI, 45.6% to 65.4%) of girls reporting receipt of at least 1 dose of the HPV vaccine, and only 66.4% (95% CI, 50.1% to 82.7%) of those girls reporting receipt of the complete three-dose regimen. Thus, HPV vaccine coverage (completed all three doses) in adolescent girls aged 13 to 17 years in Minnesota is estimated to be 35.1% (95% CI, 26.0 to 44.2%), compared to 34.8% (95% CI, 33.2% to 36.4%) nationally in 2011 [16]. Nevertheless, the 2011 three-dose coverage national estimate among girls aged 13 to 17 years falls well short of the Healthy People 2020 target of 80% for girls aged 13 to 15 years [17] and is much lower than uptake reported in Canada (50-85%), Panama (67%), a region of Mexico (67%), the United Kingdom (83%), and Australia (>70%) [18-20]. Also by way of contrast, estimates from a simulation study of the Australian population project that an HPV vaccine uptake of approximately 80% would be necessary to achieve herd immunity at the population level [21]. Although this study was based on factors specific

to Australia, the large discrepancy in actual uptake and projected uptake to achieve herd immunity is likely to be similar in the United States.

HPV vaccination uptake in boys and girls also appears to differ among sociodemographic groups. In 2011, Hispanics (65.0%, 95% CI, 60.9% to 69.1%) were statistically significantly more likely than non-Hispanic whites (47.5%, 95% CI, 45.6% to 49.4%) to have received one or more HPV vaccine doses [16]. Boys and girls who were insured privately, publicly or through the free vaccine program Vaccines for Children (VFC) were much more likely (38-55%) than the uninsured (6.4%) to have received one or more HPV vaccine doses [16].

The CDC currently monitors HPV vaccine coverage and cervical cancer screening practices by piecing together results from five national health surveys (National Survey of Family Growth (NSFG), the National Immunization Survey [22], the National Health and Nutrition Examination Survey (NHANES), the National Health Interview Survey (NHIS), and the Behavioral Risk Factor Surveillance System (BRFSS)). These surveys vary greatly in their sampling procedures, their intended target populations, the type of data that is collected, and the expected uses of the collected information. As shown in Table 2.1, four of these surveys ask respondents about either cervical cancer screening or the HPV vaccine, but fail to ask questions on both topics. Only one survey (BRFSS) asks questions regarding vaccination and screening practices in the same population of respondents. However, the information from BRFSS is restricted to four questions and does not inquire about potential barriers to screening and future vaccination plans. Importantly, sampling in these surveys is such that variations at a local level (i.e. between

counties or zip codes) cannot be adequately assessed. Additionally, these surveys have also been directed towards girls and have not inquired about the HPV vaccination practices of boys. These data are needed, as an ongoing concern is that if women who do not participate in screening are also those who are less likely to be vaccinated, disparities will continue to occur and potentially grow. Research is needed in order to determine whether women who are vaccinated are also being screened, and vice versa.

The current scarcity of data at local levels also limits researchers' ability to study the associations and patterns of HPV vaccination among youth. The only method that is currently available for assessing HPV vaccination uptake involves the patchwork of surveillance systems mentioned above which lack geographic resolution. Thus, it is not currently possible to identify detailed HPV vaccination patterns and their relationship to incident infections to estimate the long-term health effects of vaccination efforts.

2.2 HPV Burden of Disease

Approximately 79 million American men and women are currently infected with HPV, with an estimated 14 million newly infected men and women each year [23]. HPV is recognized as a necessary cause of cervical cancer, and is known to cause more than 80% of anal cancer cases in men and women [10]. HPV is also associated with several other cancers, in addition to anogenital condyloma (genital warts), respiratory papillomatosis, and intraepithelial neoplasia [24].

The most common HPV-associated mortality is cancer of the cervix, and most of the attention of clinicians and researchers has appropriately been directed toward this disease and its precursors [25]. However, HPV infection in men is of great importance as

well given that sexual transmission is the primary mode of spread to women [26-28]. Further, in the past decade, research findings have led to the recognition that HPV also causes disease in men [24]. Several cancers of the anogenital tract and upper aero-digestive tract, and their precursor lesions in men are now attributed to infection with sexually transmitted HPV [11, 29]. HPV-related outcomes have also been found to occur much more frequently among men who have sex with men, and in men infected with HIV compared to heterosexual men [25, 30-36]. Research is needed to more adequately describe the HPV infection rates among men, and to identify key risk factors that can account for the disparity of disease occurrence in male populations. Understanding HPV infections in men is therefore critical in order to reduce the morbidity associated with HPV diseases in men, as well as to reduce the risk of HPV transmission to women.

2.3 Epidemiology of HPV

There are more than 100 different types (strains) of HPV, with over 40 HPV types that infect the genital areas of men and women, most often during vaginal or anal sex [11, 37]. HPV types differ as to which type of epithelium they invade, their ability to evade immune detection, to resist immune defense mechanisms, and their oncogenic capabilities. HPV types are categorized into two groups based on their oncogenic potential: high-risk (HR-HPV) and low-risk (LR-HPV). LR-HPV types, such as types 6 or 11, can cause 1) benign or low-grade abnormalities of the cervix, 2) anogenital warts, and 3) recurrent respiratory papillomatosis (RRP) [38]. HR-HPV types, including types 16 and 18, can cause intraepithelial neoplasia of the anogenital region, including cervical, vulvar, vaginal, penile, and anal cancers as well as some oropharyngeal cancers [35, 39-

40]. HPV types 16 and 18 are considered the most highly oncogenic types as they collectively account for approximately 72% of HPV-related cancers [35].

HPV infections are primarily acquired early in sexual life [41-42]. Rates of incident HPV infection are high following first sexual intercourse [43-45]. Risk factors associated with HPV infection are related to sexual behavior. In particular, early age of first sexual relationships, high numbers of lifetime sexual partners, and sexual contacts with high risk individuals (for men, frequent contact with prostitutes and for women, frequent contacts with men with multiple sexual partners) have shown to be associated with HPV infection [46]. However, male circumcision and consistent use of condoms are factors that can reduce (but do not completely prevent) the risk of HPV transmission between sexual partners [47-48].

The prevalence of HPV infections is not only influenced by sexual activity, but also varies by age and geography, as has been shown by the International Agency for Research on Cancer (IARC) and others [49-51]. Several international studies have demonstrated that HPV acquisition and incidence peaks in young women and tends to decline with age [45, 52-54]. Whether age is also related to the duration of the infection remains to be seen. Several studies have reported that there is no influence of age on the rate of HPV clearance. Whereas other studies have reported lower clearance rates with increasing age, and some have shown fast rates of clearance in older women [55-59]. These contradictory results are likely due to variations in study populations with respect to age, geography, the type of HPV DNA test used, and other risk factors related to HPV-related outcomes.

In the United States, studies using HPV DNA testing of asymptomatic women in the general population estimate the prevalence of HPV infection to be between 2% and 44% [60]. However, prevalence of HPV infection is estimated to be the highest for both men and women during their early 20's [60-61]. Among U.S. college students, HPV prevalence has been estimated to be 24% to 55% in women and 26% to 65% in men [61]. Due to the common transmission route, many HPV types tend to be transmitted together, which results in a high proportion of concurrent infections with several types of HPV [62-64]. In addition, multiple HPV types have been detected in as many as 20% of women infected with HPV [65].

It is important to emphasize that most HPV infections are asymptomatic, transient, and are cleared naturally without treatment [11, 60, 66]. The average duration of HPV infection is estimated to last 4.3 months for LR-HPV and 9.8 months for HR-HPV among college aged women in the U.S. [67-68]. As a result, aggressive annual testing and screening for HPV infection in the general population would be extremely expensive and impractical in order to reduce HPV-associated outcomes. Moreover, an aggressive strategy of annual screening could lead to unnecessary procedures, treatments, and triage of infections that would otherwise clear naturally [69-70]. Therefore, the current strategies to limit the long-term effects of HPV rely upon early detection and screening for disease outcomes, with optional testing for HPV infection recommended in women $\geq$ 30 years in order to extend cervical cancer screening intervals.

2.4 Vaccination Against HPV

Two vaccines have been approved for use in the U.S. that are targeted at preventing HPV infection. Gardasil® (Merck & Co., Whitehouse Station, NJ USA) was approved for use by the FDA in 2006 [10, 71]. The second vaccine, Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), was approved in the fall of 2009 [12]. Gardasil® and Cervarix® both protect against HPV types 16 and 18. Gardasil® is also designed to protect against types 6 and 11, the two HPV types that cause the majority of anogenital warts [11]. Data from clinical trials have shown that both vaccines prevent vaccine type-related cervical precancers [71-72], and the quadrivalent vaccine has also been shown to prevent vaginal, vulvar, and anal precancers [73-74]. This evidence suggests that the vaccines also confer protection against HPV-related genital lesions in males aged 16 to 26 years, not just in women as was previously indicated [30-31].

Although these vaccines have shown to be safe and effective at preventing HPV infection thus far, uptake among the general population has been lower than expected (as described above) [75]. Due to the slow uptake of the HPV vaccine among women and the significant potential for preventing infection in men, the Advisory Committee on Immunization Practices (ACIP) recently amended their recommendations to include the use of the quadrivalent vaccine Gardasil® for use in young men [75]. The potential health impact and benefits that will come from this new recommendation have not yet been fully evaluated. One study recently estimated that the overall annual direct medical cost

burden of preventing and treating HPV was $8.0 billion (not including HPV vaccination or HPV testing) [76].

2.5 Detection of HPV

Randomized controlled trials conducted over the last decade suggest that HPV DNA testing could be a more effective approach to the early detection of cervical cancer for women over the age of 30 years than cytology alone [77], and that HPV self-collection (i.e., self-collection of vaginal specimens for HPV DNA testing) may be a feasible alternative to traditional clinician-collected cytology screening. Testing for HPV is more sensitive than cytology for detecting high-grade squamous intraepithelial lesions (HSIL) and invasive cervical cancer [78-88].

Sampling both the cervix and vulva-vagina, traditionally performed by a trained clinician, is the most effective method for detecting HPV infections in the female genital tract [89-90]. However, in recent years numerous studies have shown that self-collected samples are as sensitive as healthcare provider-collected samples for detection of HPV DNA [89, 91]. A recent meta-analysis of 18 studies reported that a high level of concordance of 0.87 (95%CI, 0.82 to 0.91) between self and physician sampling was obtained for detection of HPV DNA (kappa 0.66, 95%CI, 0.56 to 0.76) [90]. The prevalence difference of any HPV DNA between sampling methods was −0.5 (95%CI, −2.8 to 1.8) lower for self-collected samples. Results were similar when restricting the analysis to HR-HPV. Although most previous studies have been based on in-clinic self-collected samples that were obtained just prior to the normal patient visit, a recent study

examined at-home as well as in-clinic self-collected vaginal and clinician-collected cervical samples from a total of over 600 women age 18 to 25. Agreement between self-collected vaginal and clinician-collected combined cervical/vulva-vaginal samples was excellent [89]. Other studies confirm the accuracy and acceptability of self-sampling [92-93]. Previous studies also suggest that this at home approach is highly acceptable to women participating in screening programs [94].

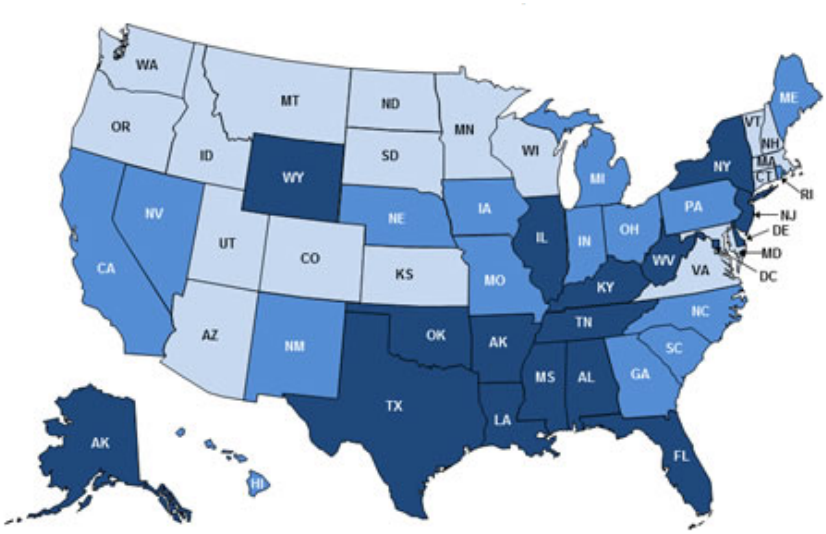
In summary, as a screening tool, self-collected samples may be comparable to clinical settings in terms of test accuracy, and may be more feasible which could increase screening coverage in the general population (and notably distinct underscreened populations may benefit from targeted efforts to use self-collected sampling) than clinician-performed sampling [89]. Self-sampling would remove the need for a clinician and encourage screening coverage among women not attending clinic based cervical cancer screening. Furthermore, with HPV typing and the availability of prophylactic HPV vaccines, it is important to determine the population-level impact of vaccines on the prevalence of HPV types that are and are not targeted by vaccines.

2.6 Conclusion

The tremendous disease burden due to HPV infections and the potential benefits of vaccination are only beginning to be understood. In order to mitigate major gaps in knowledge regarding HPV vaccines, it is imperative that data be collected at local levels to better estimate their impact and reach. Understanding the patterns of where HPV-related diseases occur will help shape HPV prevention strategies (i.e. vaccine campaigns

and policies) and assist in predicting the actual burden of HPV-related disease. Using modern methods and venues, such as self-collected sampling and HPV DNA tests, to reach underserved men and women is essential in order to improve screening uptake and increase the treatment of disease. These modern methods provide more flexibility than traditional clinical settings and permit targeted strategies toward underscreened men and women. These tailored approaches will have the greater impact as they can focus on the at-risk and underserved populations instead of doing more among the majority of the population who are already at a reduced risk of HPV-associated diseases.

Figure 2.1. Map of HPV-associated cervical cancer rates by state, 2012.

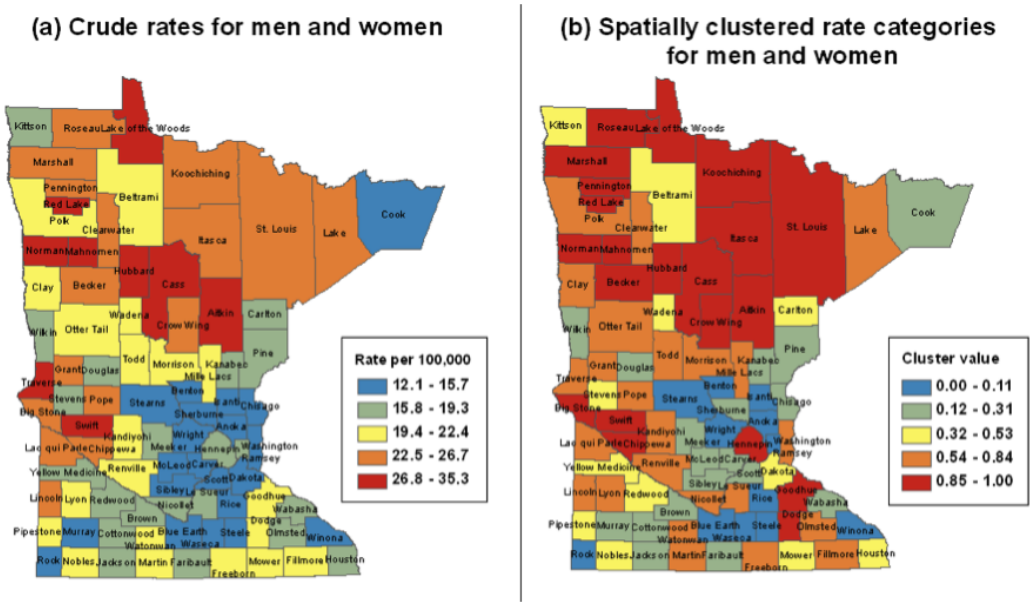


Color on Map	Interval	States
	5.09 to 6.57	Arizona, Colorado, Connecticut, Idaho, Kansas, Maryland, Massachusetts, Minnesota, Montana, New Hampshire, North Dakota, Oregon, South Dakota, Utah, Vermont, Virginia, Washington, and Wisconsin
	6.58 to 8.07	California, Georgia, Hawaii, Indiana, Iowa, Maine, Michigan, Missouri, Nebraska, Nevada, New Mexico, North Carolina, Ohio, Pennsylvania, Rhode Island, and South Carolina
	8.08 to 10.13	Alabama, Alaska, Arkansas, Delaware, District of Columbia, Florida, Illinois, Kentucky, Louisiana, Mississippi, New Jersey, New York, Oklahoma, Tennessee, Texas, West Virginia, and Wyoming

Rates are per 100,000 females and are age-adjusted to the 2000 U.S. standard population.

Data are from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology and End Results Program, and meet criteria for high data quality.

Figure 2.2. Crude rates and spatially clustered rate categories of HPV-associated cancers in men and women by county in Minnesota, 1998-2007.



Clustered values can range from 0 to 1, with values closer to 1 indicating clustering of high rate values (red) and values closer to 0 representing clusters for low rate values (blue). Coordinate System: NAD 1983 HARN StatePlane Minnesota Central FIPS 2202.

Table 2.1. Comparison of five national surveys regarding cervical cancer screening and HPV vaccination questions among women.

Survey	Age of Female Respondents	Cervical Cancer Screening	HPV Vaccine Receipt	HPV Vaccine Barriers & Intentions	Data Extent
NHANES	14-59 yrs	No	Yes	No	State/Nation
NIS	13-17 yrs	No	Yes	Yes	State/Nation
NSFG	15-44 yrs	No	Yes	Yes	State/Nation
NHIS	18-49 yrs	Yes	No	No	Nation[a]
BRFSS	18-49 yrs	Yes	Yes	Yes	State/Nation

[a]Some state level data are available
Abbreviations used: NHANES, National Health and Nutrition Examination Survey; NIS, National Immunization Survey; NSFG, National Survey of Family Growth; NHIS, National Health Interview Survey; BRFSS, Behavioral Risk Factor Surveillance System

Chapter 3. Manuscript 1: Facebook Recruitment for an Online Survey to Estimate Geographic Variation in Human Papillomavirus Vaccine Uptake in Men and Women

3.1 Overview of Manuscript 1

The objective of Manuscript 1 was to describe HPV vaccination and cancer screening practices in the Twin Cities Metropolitan Area. Currently, no data has been collected that captures HPV vaccination status, cancer screening practices, and barriers to HPV vaccination and cancer screening services within the same survey instrument. This is important because current strategies are based on a patchwork of incomplete data from several surveillance systems. Obtaining information on cancer screening practices and HPV vaccination within the same study population may lead to a better understanding of who is not receiving these services and where these services could be used to reduce HPV-related disease.

The goal of this pilot project was to analyze self-reported questionnaire data from the Survey of Minnesotans About Screening and HPV (SMASH) Study to better understand uptake of the HPV vaccine and cancer screening, and characteristics associated with not receiving these services. The SMASH Study recruited men and women in Minnesota via Internet-based social media to complete an online survey regarding HPV vaccination status, cancer screening practices and potential barriers to receiving these services based on the participants' place of residence. The aim of this project was to demonstrate the feasibility and cost of using the Internet to recruit and administer a survey to a representative sample from the Twin Cities Metropolitan Area

(Aim 1). Manuscript 1 also describes the characteristics of study participants and estimates the prevalence of HPV vaccination in the Twin Cities Metropolitan Area and compares them to state and national level estimates (Aim 2).

3.2 Summary

Background: Federally funded surveys of human papillomavirus (HPV) vaccine uptake are important for pinpointing geographically based health disparities. Although national and state level data are available, local (i.e. county and zip code level) data are not due to small sample sizes, confidentiality concerns, and cost. Local level HPV vaccine uptake data may be feasible to obtain by targeting specific geographic areas through social media advertising and recruitment strategies, in combination with online surveys.

Objective: To use Facebook based recruitment and online surveys to estimate local variation in HPV vaccine uptake among young men and women in Minnesota.

Methods: From November 2012 to January 2013, men and women were recruited via a targeted Facebook advertisement campaign to complete an online survey about HPV vaccination practices. The Facebook advertisements were targeted to recruit men and women by location (25 mile radius of Minneapolis, Minnesota, United States), age (18-30 years), and language (English).

Results: Of the 2,079 men and women who responded to the Facebook advertisements and visited the study website, 1,003 (48.2%) enrolled in the study and completed the survey. The average advertising cost per completed survey was $1.36. Among those who reported their ZIP code, 881 out of 972 (90.6%) of the participants

lived within the *a priori* geographically defined study area. Receipt of ≥1 dose of HPV vaccine was reported by 351 of 535 women (65.6%), and by 45 of 361 men (12.5%). These results differ from previously reported Minnesota state level estimates (53.8% for young women and 20.8% for young men) and from national estimates (34.5% for women and 2.3% for men).

Conclusions: This study shows that recruiting a representative sample of young men and women based on county and zip code location to complete a survey on HPV vaccination uptake via the Internet is a cost-effective and feasible strategy. This study also highlights the need for local estimates to assess the variation in HPV vaccine uptake, as these estimates differ considerably from those obtained using survey data that is aggregated to the state or federal level.

3.3 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the U.S. [1], and is the necessary cause of cervical cancer [2]. HPV infections are also associated with other cancers (e.g. anogenital and oropharyngeal) as well as genital warts [3-4]. In total, it is estimated that 5.2% of cancers in men and women worldwide are attributable to HPV [35].

Two vaccinations against HPV infection are currently licensed in the U.S. The vaccinations were originally licensed for use in girls, but as of October 2011, the Advisory Committee on Immunization Practices (ACIP) extended their recommendation of the quadrivalent vaccine to include both boys and girls aged 11 or 12 years old [12, 14]. However, vaccine uptake has been far lower than expected, with only about half of

eligible young women receiving at least one dose of the vaccine [15]. Initiation of the HPV vaccine has been shown to be higher among minority adolescent girls, however completion of the three-dose series is substantially lower among blacks and Hispanics compared to whites [95]. Although male vaccination data are very limited (due to a later date of approval of the HPV vaccine for boys), racial and income differences in terms of vaccine series initiation and completion have also been observed among adolescent boys [96].

Previous research on HPV vaccine coverage has utilized publicly available data from five national health surveys (National Survey of Family Growth, National Immunization Survey - Teen, National Health and Nutrition Examination Survey, National Health Interview Survey, and the Behavioral Risk Factor Surveillance System) [97-101]. These surveys are designed to gather information on a variety of health topics and only ask a few questions regarding HPV vaccination. However, none of these surveys addresses HPV vaccination and related practices such as cervical cancer screening and potential barriers to screening or vaccination. In addition, due to the small number of responses in many geographic areas, local data from these surveys are routinely suppressed and aggregated to state boundaries in order to protect the confidentiality of survey respondents which means that variations at a local level (i.e. between counties or ZIP codes) cannot be adequately assessed. Further, these surveys have, to date, primarily surveyed adolescent girls; HPV vaccination practices of adolescent boys are limited [15].

The Internet provides a unique point of contact to reach young adults for health research. Several studies have demonstrated that Internet-based research can be used to elicit high response rates at a fraction of the cost of traditional recruitment methods [102-104]. In addition, it has been shown that when compared to in-person interviews, Internet-based surveys have the potential to reach more respondents, include otherwise inaccessible populations, and to reduce bias in responses as respondents may be willing to report more sensitive information online compared to in-person interviews [105-110]. A number of studies have also shown that recruitment via Facebook (the leading social media site with more than one billion active users worldwide) can be used to enroll representative samples of the general population [102, 111-114]. This combination of reach, utility, and reduced cost indicates that social media networks can be a cost-effective medium for research.

The objective of this study was to estimate HPV vaccination practices among a local population of young adult men and women using an Internet-based recruitment strategy.

3.4 Research Methods

Study Population

Men and women from Minnesota were surveyed about their HPV vaccination practices via the Internet from November 21, 2012 through January 31, 2013. Participants were English-speaking, aged 18 to 30 years, had a Facebook account, and resided in the greater Twin Cities Metropolitan Area (i.e. within 25 miles of downtown Minneapolis, MN). This age range was used to target men and women who were eligible to receive the

HPV vaccine, participate in cervical cancer screening (women), and able to provide informed consent. The Twin Cities Metropolitan Area was selected due to heterogeneity of HPV-related cancer incidence rates exhibited in this area during the past 15 years, the high concentration of colleges and universities, and the large population of 18 to 30 year olds residing in this area [9]. The University of Minnesota Institutional Review Board approved this study.

Facebook Recruitment Campaign

Participants were recruited online via Facebook advertisements (Figure 3.1). Tailored advertisements were used to target Facebook users that had profiles that matched the study inclusion criteria. These advertisement criteria were adjusted as needed to achieve a balanced sample of participants by ZIP code. Facebook uses an advertisement algorithm that automatically selects the best advertisement to display based on its performance and the advertiser's bid [115]. All advertisements were approved by Facebook. For this study, multiple advertisements were submitted for auction simultaneously to create a continuous recruitment window in the event that a particular advertisement performed poorly. Bidding prices and advertisement availability (advertisements can be paused and released at the discretion of the advertiser) were monitored daily and adjusted as necessary until the intended number of completed questionnaires was obtained. When a Facebook user clicked on the study advertisement, they were automatically redirected to the secure study website.

The Facebook Ads Manager was used to track the total number of impressions (each time an advertisement was displayed), the number of times an ad was clicked, the average cost-per-click, and the number of people reached (i.e. the number of Facebook

users that had an opportunity to view one of the study advertisements). Google Analytics software (Mountain View, CA, USA) was used to tabulate the total number of visits, the unique visits, the average duration of visits, and the bounce rate (the percentage of visitors who visit a website and leave the site without further browsing) of the study website.

Study Procedures

After providing consent, study participants were asked to self-report their age, gender, ZIP code of their home address, race/ethnicity, highest level of education attained, attendance at religious services, political preferences, sexual orientation, their awareness of HPV, and whether or not they had received the HPV vaccine. Conditional upon participants' responses, follow-up questions regarding the number of shots received, the vaccine type (quadrivalent/bivalent), and reason(s) for not having received the vaccination, as well as future vaccination intentions were administered. Female participants were also asked a series of adaptive questions about past cervical cancer screening. The survey questions regarding HPV vaccination and cancer screening that we used in this study were questions used in the five national surveys mentioned above, in order to facilitate comparisons between studies. Participants were not required to answer every question and could exit the survey at any time. Computer Internet Protocol (IP) addresses were tracked and multiple entries from the same IP address were not accepted. Additionally, survey responses that contained repeated email addresses across multiple survey attempts (n=86) or were only partially completed (n=8) were not accepted. The survey was anonymous and was administered using the online survey assessment tool SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA). Eligible

respondents who provided informed consent and completed the online survey were emailed an electronic gift card in the amount of $20 to Target.com®.

3.5 Results

Of the 2,079 men and women who were recruited via Facebook and visited the study website, 1,003 (48.2%) enrolled in the study and completed the survey. Targeted advertising within Facebook based on geographic and age criteria limited the number of ineligible participants (4.4% of all survey attempts) who attempted to access the survey. In total, 86 survey attempts (7.5% of all survey attempts) were identified as duplicate surveys, indicating that an individual attempted to complete the survey more than once (Figure 3.2). Facebook advertising and recruitment resulted in an average advertising cost of $1.36 per completed survey. In addition, 881 out of the 972 study participants (90.6%) who self-reported their ZIP code were located within the recruitment target area (i.e. located within a 25-mile radius of downtown Minneapolis, Minnesota) (Figure 3.3).

A total of 1,003 participants (557 women and 446 men) completed the online survey. Characteristics of the study population are presented in Table 3.1. With respect to race/ethnicity, the study population was broadly similar to that of 18 to 34 year-olds in the greater Minneapolis-St. Paul Metropolitan Area based on U.S. Census data. However, due to the age and geographic inclusion and exclusion criteria, the study population was more educated than the general population of 18 to 34 year-olds in the Minneapolis-St. Paul Metropolitan Area. In all, 44.2% of respondents (396 of the 896) who knew of the HPV vaccine had been vaccinated against HPV (i.e. received ≥1 dose of HPV vaccine), with 65.6% of women (351 out of 535) having been vaccinated with ≥1

dose of HPV vaccine compared to 12.5% of men (45 out of 361). Completion of the HPV vaccine series (i.e. receipt of all 3 doses) was reported by 74.9% of women (263 out of 351) and 22.2% of men (10 out of 45) who had ever received an HPV vaccine. Among the 351women who had received ≥1 dose of HPV vaccine, 265 (75.5%) had also received at least one Pap smear in their lifetime.

Of the 479 unvaccinated men and women, 403 (84.1%) were not interested or were unsure about receiving the vaccine in the future. The main reasons cited were: "not necessary or not needed" (45.6%), not sexually active (14.2%), insufficient knowledge about HPV or the vaccine (8.9%), concerns about safety or side effects (7.8%), cost of the vaccine (6.8%), already infected with HPV (6.1%), in a monogamous relationship (3.5%), and too old for the vaccine (1.3%) (Table 3.2). Eleven men (2.8%) reported that the vaccines were not intended for use in men. When participants were allowed to report all of the reasons that they would not receive the vaccine in the following 12 months, the most frequently cited responses were: "not necessary or needed" (26.8%), provider did not recommend the vaccine (13.5%), cost of the vaccine (13.0%), not sexually active (10.9%), and concerns about the safety or side effects of the vaccine (9.7%).

3.6 Discussion

In this study we found that recruiting a locally representative sample of young adults via the Internet to participate in a survey about HPV vaccination was cost-effective and efficient. Approximately half of the 2,079 individuals that clicked on an advertisement and visited our study website participated and completed our survey at an estimated advertising cost of $1.36 per enrolled participant. Consistent with other

studies, this study found that using the Internet and in particular social media sites such as Facebook, can be successful for recruiting and engaging young adults populations for health research [102-104]. This method of recruitment is particularly noteworthy given declining response rates from traditional recruitment techniques such as random digit dialing or mailed surveys [116-118]. In addition to higher participation rates, the targeted advertising features embedded within social media websites drastically reduce costs associated with identifying and reaching a large pool of eligible participants [111, 113-114]. The targeted advertising used in this study also allowed us to collect data within an accelerated timeline (e.g. pilot testing of a specific intervention) from a specific geographic location.

Notably, the characteristics of our study population were similar to those of the source population. An estimated 90% of Internet users aged 18-29 in the U.S. access social media sites (71% accessed Facebook) in 2013, thus this finding is likely attributable to the wide reach of social media recruitment [119]. An exception however, was that our study population was more educated than the general population in the Minneapolis-St. Paul Metropolitan Area which may be due to the large number of colleges and universities in this area. However, it cannot be ruled out that people with lower education were less likely to access Facebook and view the advertisements although other studies have shown that lower income and less educated participants are as likely to participate in Internet-based research studies as those who with higher incomes and higher levels of education [114, 120-121].

Other limitations include the fact that the survey responses were self-reported by persons over the Internet and may be subject to under or over-reporting. However, other Internet-based studies have shown increased self-disclosure and reporting with online surveys, which may reduce potential response biases (e.g. interviewer bias or social desirability) [105, 107]. Additionally, there was no fail proof method to ensure that survey responses were unique and there remains a small probability that some participants responded more than once.

In this study we were also able to collect detailed HPV vaccination data, including participation in screening (for women) and potential barriers to receiving these services among a representative sample of men and women in a defined local geographic area. National surveys including the Behavioral Risk Factor Surveillance System, the National Health Interview Survey, and the National Immunization Survey-Teen, do not simultaneously assess these factors within the same respondents in their populations. Additionally, these (and other) national surveys aggregate or suppress responses due to participant identification concerns and consequentially local variation and patterns may be obscured. However, HPV vaccine policies, availability, costs, financial assistance, and education materials vary widely across states or even more defined geographic regions [122]. As a result, variation at state and national levels may not reflect the variation in HPV vaccine uptake occurring at a local level.

Of note, the proportion of all adults in this study who had been vaccinated against HPV (i.e. received at least one dose of an HPV vaccine) was 44.2% (65.6% for women and 12.5% for men). These estimates are much higher than the HPV vaccine coverage

estimates from the 2012 National Health Interview Survey (NHIS) for women (34.5%) and men (2.3%) aged 19 to 26 [123]. Although the results for women are more similar to those obtained from the National Immunization Survey – Teen for girls (53.8%), the estimate for men is much lower than the NIS-Teen estimate for boys (20.8%) aged 13 to 17 who received at least one dose of HPV vaccine in 2012 [15]. Although the differences in the observed rates may be partially explained by the sampling frame, response rates, or the small number of eligible respondents who received the HPV vaccine question series in the national surveys, the estimates of HPV vaccine uptake are noticeably different from the current study.

To our knowledge, this is the first study to estimate local level vaccination uptake among young men in the United States. Understanding the local variation and patterns of HPV vaccination of young men could serve to identify areas where HPV infection-related health disparities may continue if neglected. In particular, the online survey also allowed us to collect data on sexual orientation which in turn would allow us to understand whether men who have sex with men, who are at high risk of HPV-related anal cancer, are receiving the vaccine and to also determine whether reductions in the overall risk of HPV infection will affect transmission to females [24, 124].

In conclusion, the results from this study suggest that more detailed and local assessments of HPV vaccine uptake are necessary as estimates vary greatly from national surveys. In addition, recruiting young adults via the Internet is efficient, cost-effective, and can produce a representative sample of the target population. Future work is needed

to understand the pattern of HPV vaccine uptake at local levels in order to identify areas that may be best served by vaccine programs.

Table 3.1. Selected study participant characteristics compared to U.S. Census estimates for Minneapolis and St. Paul, Minnesota.[a]

	Study Participants			Census Data
	Men (N=446)	Women (N=557)	Total (N=1,003)	Mpls./St. Paul (%)
Mean age (years)	23	23	23	18 to 34
Race *n* (%)				
White	384 (86.3)	457 (82.3)	841 (84.1)	78.1
Black	17 (3.8)	33 (5.9)	50 (5.0)	8.6
Asian	30 (6.7)	30 (5.4)	60 (6.0)	7.7
AI or AN[b]	2 (0.4)	7 (1.3)	9 (0.9)	0.7
Native Hawaiian or PI[c]	1 (0.2)	3 (0.5)	4 (0.4)	0.03
Other	11 (2.5)	25 (4.5)	36 (3.6)	4.9
Ethnicity *n* (%)				
Hispanic	15 (3.4)	19 (3.4)	34 (3.4)	2.6
Non-Hispanic	427 (96.6)	533 (96.6)	960 (96.6)	97.4
Education *n* (%)				
<High School	2 (0.4)	0 (0.0)	2 (0.2)	1.9
Some High School	6 (1.3)	8 (1.4)	14 (1.4)	7.9
High School Graduate	36 (8.1)	36 (6.5)	72 (7.2)	22.1
Some College/Tech. School	190 (42.7)	209 (37.6)	399 (39.9)	36.7
College Graduate	167 (37.5)	237 (42.6)	404 (40.4)	24.9
Graduate School	44 (9.9)	66 (11.9)	110 (11.0)	6.6
Political Preferences *n* (%)				
Very Conservative	19 (4.3)	9 (1.6)	28 (2.8)	n/a[d]
Conservative	84 (18.9)	60 (10.8)	144 (14.4)	n/a
Moderate	157 (35.4)	164 (29.5)	321 (32.1)	n/a
Liberal	139 (31.3)	225 (40.5)	364 (36.4)	n/a
Very Liberal	45 (10.1)	97 (17.5)	142 (14.2)	n/a
Religious Attendance *n* (%)				
More than once per week	23 (5.2)	23 (4.1)	46 (4.6)	n/a
Once per week	55 (12.3)	82 (14.8)	137 (13.7)	n/a
Once or twice per month	56 (12.6)	86 (15.5)	142 (14.2)	n/a
A few times per year	114 (25.6)	118 (21.3)	232 (23.2)	n/a
Seldom	97 (21.7)	103 (18.6)	200 (20.0)	n/a
Never	101 (22.6)	143 (25.8)	244 (24.4)	n/a
Sexual Orientation *n* (%)				
Heterosexual	398 (91.5)	499 (91.9)	897 (91.7)	n/a
Homosexual, gay, or lesbian	33 (7.6)	11 (2.0)	44 (4.5)	n/a
Bisexual	4 (0.9)	33 (6.1)	37 (3.8)	n/a

[a]Data are 5-year estimates for 18 to 34 year-olds in the Minneapolis-St. Paul Metropolitan Area as described in the 2006-2010 American Community Survey of the United States Census Bureau.
[b]American Indian or Alaska native
[c]Pacific Islander
[d]not available

Table 3.2. Selected survey responses regarding vaccination against human papillomavirus.

Survey Question	Men (N=446)	Women (N=557)	Total (N=1003)
	n (%)	n (%)	n (%)
Ever heard of HPV[a]			
Yes	409 (93.0)	536 (96.8)	945 (95.1)
No	31 (7.0)	18 (3.2)	49 (4.9)
Ever heard of HPV vaccine			
Yes	361 (82.4)	535 (96.6)	896 (90.3)
No	77 (17.6)	19 (3.4)	96 (9.7)
Ever had HPV vaccine			
Yes	45 (13.0)	351 (66.5)	396 (45.3)
No	302 (87.0)	177 (33.5)	479 (54.7)
Number of HPV shots			
1 shot	11 (24.4)	31 (8.8)	42 (10.6)
2 shots	14 (3.9)	38 (10.8)	52 (13.1)
3 shots (complete vaccine series)	10 (22.2)	263 (74.9)	273 (68.9)
Don't know	10 (22.2)	19 (5.4)	29 (7.3)
Vaccine receipt[b] (next 12 mo)			
Very likely	7 (2.3)	13 (7.3)	20 (4.2)
Somewhat likely	26 (8.6)	30 (16.9)	56 (11.7)
Not too likely	75 (24.8)	47 (26.6)	122 (25.5)
Not likely at all	173 (57.3)	84 (47.5)	257 (53.7)
Not sure/don't know	21 (7.0)	3 (1.7)	24 (5.0)
Reason no HPV vaccine[b] (next 12 mo)			
Not needed or necessary	140 (52.4)	40 (31.3)	180 (45.6)
Not sexually active	33 (12.4)	23 (18.0)	56 (14.2)
Knowledge[d]	25 (9.4)	10 (7.8)	35 (8.9)
Safety concerns/side effects	9 (3.4)	22 (17.2)	31 (7.8)
Costs	13 (4.9)	14 (10.9)	27 (6.8)
Already have HPV	19 (7.1)	5 (3.9)	24 (6.1)
Monogamous	8 (3.0)	6 (4.7)	14 (3.5)
Other[e]	6 (2.2)	6 (4.7)	12 (3.0)
Not for men	11 (4.1)	0 (0.0)	11 (2.8)
Too old	3 (1.1)	2 (1.6)	5 (1.3)

[a]Human papillomavirus
[b]Responses presented are for the 479 individuals who reported not having been vaccinated against HPV.
[c]This question was asked among participants who responded "not too likely," "not likely at all," or "not sure/don't know" when asked if they would receive the HPV vaccine in the next 12 months.
[d]Don't know about HPV or HPV vaccine
[e]Responses included "fear of needles," "too busy/no time," "don't use vaccines," or "already sexually active."

Figure 3.1. Examples of Facebook advertisements.

Figure 3.2. Manuscript 2 recruitment summary flowchart.

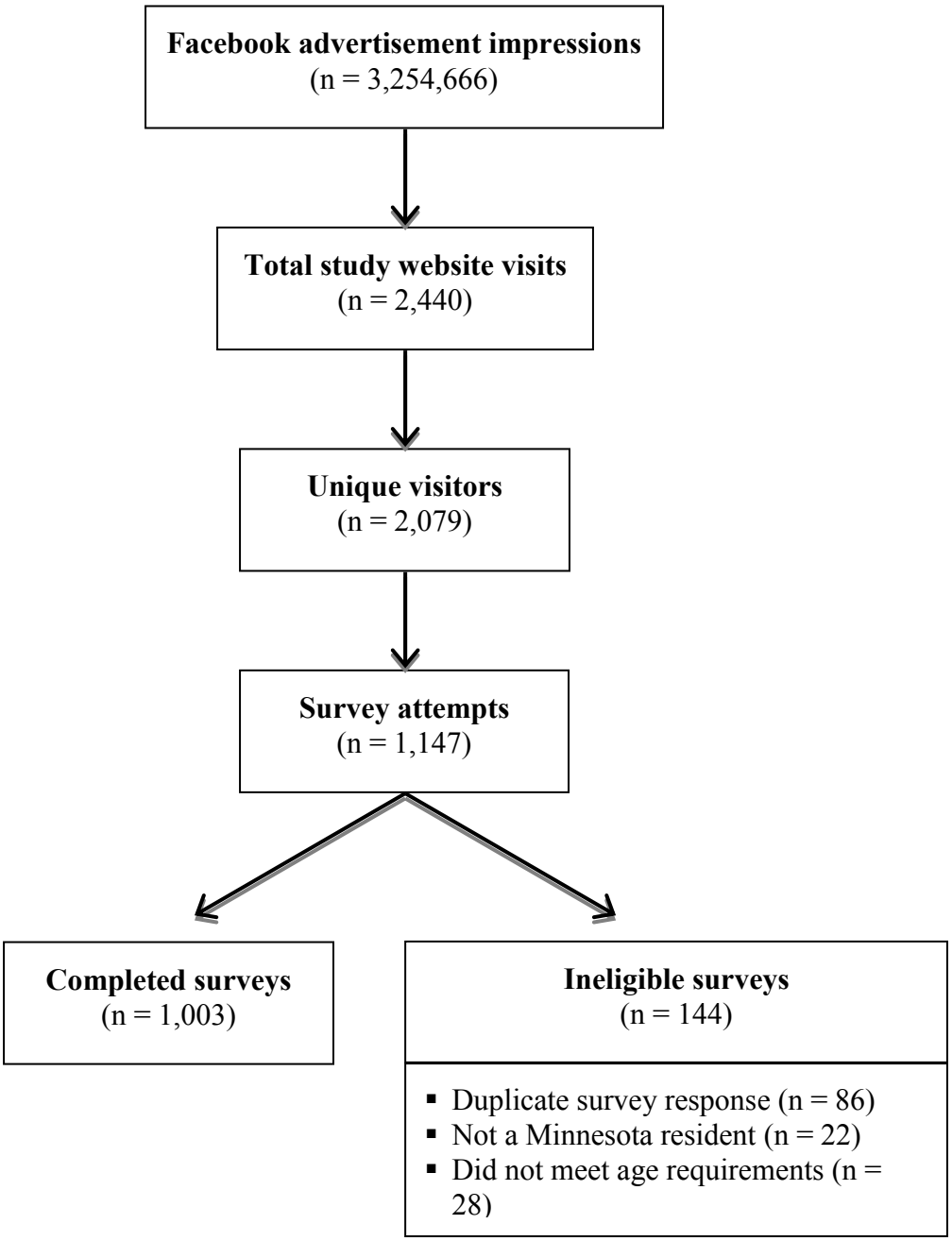
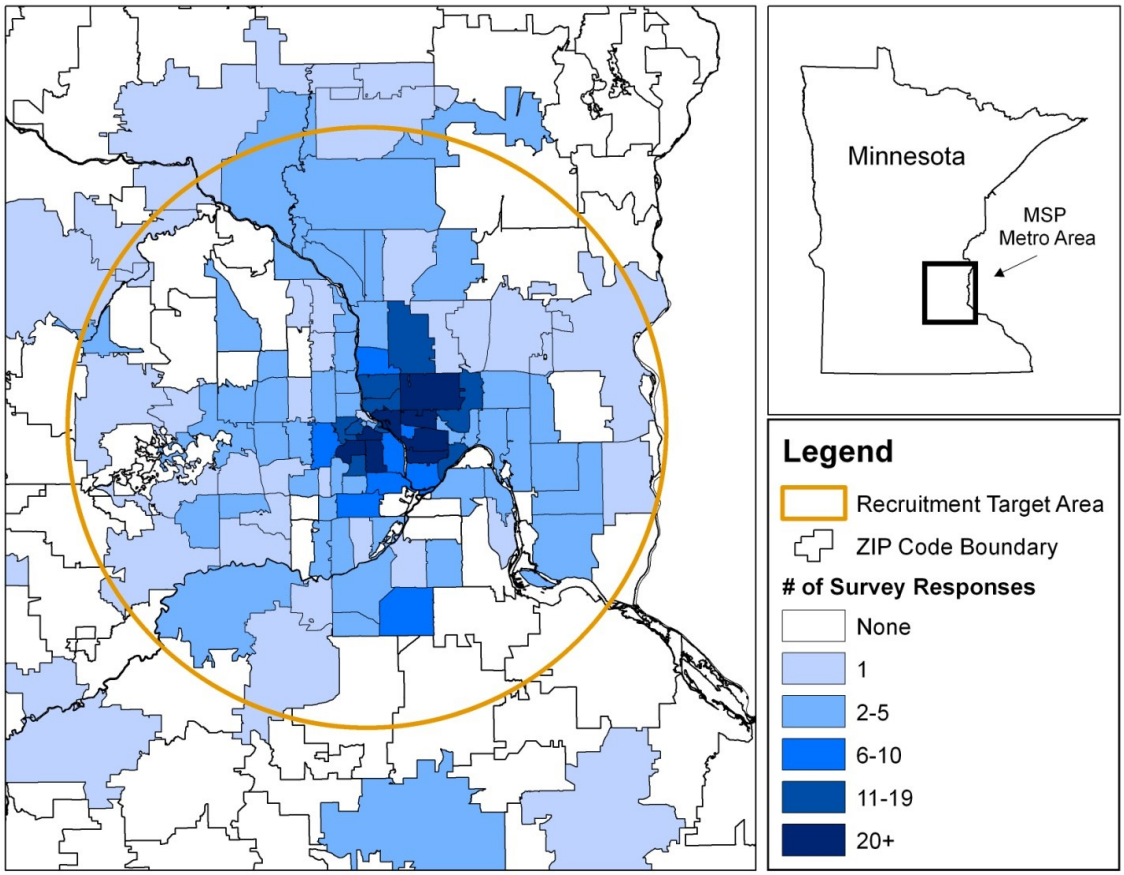


Figure 3.3. Map of the recruitment target area and the number of completed surveys by ZIP code.



The recruitment target area for this study was a 25-mile radius from downtown Minneapolis, Minnesota (represented by the orange circle). Of the 972 participants that reported their ZIP code, 881 (90.6%) lived within the recruitment study area. MSP indicates Minneapolis-St. Paul.

Chapter 4. Manuscript 2: Geographic Variation in Human Papillomavirus Vaccine Uptake at the ZIP Code Level in Minnesota.

4.1 Overview of Manuscript 2

The objective of Manuscript 2 was to describe and evaluate the distribution of HPV vaccination practices by ZIP code in the Twin Cities Metropolitan Area. This study aggregated participant responses from the SMASH Study (described in Manuscript 1) by ZIP code in order to estimate and map the distribution of HPV vaccination uptake in the Twin Cities Metropolitan Area (Aim 3). Understanding the effects of geographic variation and the impact of residential patterns on HPV vaccine receipt will more fully identify where disparities exist and where vaccination strategies may yield the most benefit.

Spatial statistics permit the analysis of distributions, patterns, processes, and relationships across space and time. While there are some similarities between spatial and non-spatial (traditional) statistics in terms of concepts and objectives, spatial statistics are unique in that they were developed specifically for use with geographically referenced data. Unlike traditional non-spatial statistical methods, spatial statistics explicitly incorporate space (proximity, area, connectivity, and/or other spatial relationships). For this manuscript, spatial logistic models were employed to determine the spatial pattern of HPV vaccination by ZIP code in the Twin Cities Metropolitan Area.

4.2 Summary

Background: Research describing the geographic variability in human papillomavirus (HPV) vaccination uptake at the state or county level is limited, has relied on data collected from large national surveillance programs and has, to date, not accounted for spatial autocorrelation (i.e. the degree to which data values are related based on their distance from one another). A concern with assuming national data can be used to infer local variation in HPV vaccine uptake is that use of such data may mask significant variability and potential disparities at the local level.

Objective: To determine if there is geographic variation, and if so, to examine the pattern in HPV vaccine uptake using ZIP code level data, and to identify predictors of vaccination while accounting for spatial autocorrelation.

Methods: Data on HPV vaccination at the ZIP code level were collected for 760 individuals nested within 99 ZIP codes surrounding the downtown area of Minneapolis, Minnesota. Proper conditional autoregressive (CAR) models, which account for spatial dependence, were used to identify predictors associated with receipt of HPV vaccination.

Results: In all, 46.2% of participants had received at least one dose of HPV vaccine (67.7% of women reported having been vaccinated compared to 13.0% of men). HPV vaccination was found to exhibit strong spatial dependence ($\hat{\rho} = 0.9966$). Accounting for spatial dependence, older age (OR = 0.76, 95% CI = 0.71-0.82) and male gender (OR=0.03, 95% CI = 0.02-0.05) were negatively associated with vaccination, while moderate (OR = 3.24, 95% CI = 1.62-6.49) and liberal political preferences (OR =

5.32, 95% CI = 2.68-10.58) were found to be significant positive predictors of HPV vaccination.

Conclusions: This study highlights the need to account for spatial dependence when looking at geographic variation in HPV vaccination. This study also underscores the need for more detailed data collected at the local level as ZIP code level patterns of HPV vaccine receipt were found to differ significantly from aggregated state and national patterns.

4.3 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the U.S. [1], and is the necessary cause of cervical cancer [2]. HPV infections are also associated with other cancers (e.g. anogenital and oropharyngeal) as well as genital warts [3-4]. Since mid-2006, the Advisory Committee on Immunization Practices (ACIP) has recommended routine vaccination of adolescent girls aged 11 or 12 years with the three-dose HPV vaccine series [13]. In October 2011, the ACIP extended their recommendation of the quadrivalent vaccine to include boys aged 11 or 12 years old [12, 14]. The ACIP also recommends catch-up vaccination for those aged 13 to 26 years. However, HPV vaccination uptake has been far lower than expected, with only 53.8% of girls and 20.8% of boys aged 13-17 years and 34.5% of women and 2.3% of men aged 19-26 years receiving at least one dose of the vaccine as of 2012 [123, 125]. Despite lower than anticipated vaccine uptake, recently published HPV vaccine serosurvey results show significant reductions in HPV prevalence, and reductions in HPV-associated cancer incidence of approximately 70% are predicted in the coming decades [72-74, 126-127].

Initiation of the HPV vaccine (i.e. receiving at least one dose) has been shown to be higher among minority adolescent girls; however, completion of the three-dose series is substantially lower among blacks and Hispanics compared to whites [95]. Although male vaccination data are very limited, racial and income differences have also been observed among adolescent boys [96]. Disparities in receipt of the HPV vaccine have also been found to be associated with access to healthcare, clinical provider characteristics, and parental perceptions of the HPV vaccine [96, 99, 128-132].

Research on the geographic variability of HPV vaccination is limited, and has relied on data collected from large national surveillance programs to estimate uptake at the state or county levels [100-101, 133]. These national data on geographic variation in HPV uptake may mask a considerable amount of variability at more localized levels. Further, a major limitation of these geographic studies is that they do not account for the areal units on which data are recorded, commonly referred to as the spatial structure of the data. Data collected in this manner typically exhibit spatial dependence (also referred to as spatial autocorrelation), with observations from areal units close together tending to have similar values [134]. Although a proportion of spatial dependence may be modeled by including known covariate risk factors (i.e. age, race, sex) in a traditional regression model, it is common for spatial structure to not be accounted for and to remain in the residuals even after accounting for these covariate effects (i.e. to be spatially confounded) [134]. For example, one study noted several individual factors that were predictive of receipt of HPV vaccination, including geographic region of residence, however they did not fully account for spatial dependence as they used a categorical variable to account for

geographic differences in uptake [135]. Another study that analyzed geographic variation in HPV vaccine uptake used a weighting scheme to account for the complex selection of study participants, yet ignored accounting for the spatial dependence between geographic regions [101]. Thus, these studies inherently assume that factors associated with HPV vaccine uptake are homogeneous across areal units (i.e. states or counties). To date, the intra-county geographical variation of HPV vaccination has not been examined while accounting for spatial dependence. Documenting geographic variation in vaccine disparities at local levels may help to identify specific areas with the largest disparities in HPV vaccine uptake (after accounting for spatial dependence) thereby informing outreach efforts, and may also provide new hypotheses regarding the underlying determinants of geographic patterns in uptake.

The objective of this study was to use HPV vaccination data measured at the ZIP code level to identify geographic variation in vaccine uptake, and to identify predictors of receipt of HPV vaccination while accounting for spatial dependence.

4.4 Methods

Data

This study utilized data collected on 1,003 participants from the Survey of Minnesotans About Screening and HPV (SMASH) study, which is a cross-sectional study of English-speaking men and women aged 18-30 years from the Twin Cities Metropolitan Area of Minnesota (Manuscript 1). Briefly, from November 2012 to January 2013, targeted advertisements were displayed on the social networking site Facebook™ to men and women who met the study eligibility criteria (as specified in their

user profiles). Men and women who clicked on a study advertisement were redirected to the secured SMASH study website and invited to participate in an online survey. After providing consent, participants were asked to answer questions regarding HPV vaccination, cancer screening, and barriers/intentions regarding receipt of either.

The response to the question "*Have yo*u *ever received an HPV vaccine?"* was used as the current study's outcome variable for HPV vaccination status. Individuals (n=128) who responded *don't know*, refused, or who did not respond to this question were excluded from the study. Similarly, individuals who did not report their ZIP code (n=3), or who reported a ZIP code outside of the predetermined 25-mile radius of downtown Minneapolis, Minnesota (n=112) were excluded from the study in order to focus on this diverse metropolitan population. The resulting study sample consisted of 760 (75.8% of total enrolled) men and women nested within 99 ZIP codes.

Spatial Data Analysis

Spatially dependent data violate the independence assumption required for generalized linear models. As such, ignoring the dependence of spatial data can lead to underestimation of standard errors, resulting in overly narrow confidence interval estimates and, consequently, incorrect statistical inference [136]. To account for residual dependence it is standard practice to augment the linear predictor with a spatial random effect, as part of a Bayesian hierarchical model [137]. These random effects typically take the form of a conditional autoregression (CAR), which introduces spatial dependence through the adjacency structure of areal units [137]. CAR models are generally applied in a Bayesian setting, where inference is based on Markov-chain Monte Carlo (MCMC) simulation [138].

To accommodate the potential spatial dependence of HPV vaccination, we implemented a spatial logistic regression model using ZIP code as the areal unit of analysis. Assume Y_i is the number of respondents who were vaccinated against HPV out of the total N_i sampled in each ZIP code j. The outcome can be modeled as a binomial response $Y_{ij} \sim bin(p_{ij}, N_{ij})$ such that p_{ij} is the true vaccine uptake proportion of individual i within a selected ZIP code j. The proportions were smoothed using the following model,

$$\text{logit}(p_{ij}) = \alpha + \beta X_{ij} + s_j \quad (1)$$

where α is an intercept, which is interpreted as an overall log-odds coverage for all areas; β are the effects of the covariates X_{ij} in the model; and the s_j are spatially dependent random effects, such that neighboring areas have a similar vaccine uptake proportion. The parameter ρ (termed rho) is a spatial autocorrelation parameter that is estimated as part of the spatially dependent random effect s_j [137]. Rho describes the strength of spatial dependency, with 0 corresponding to spatial independence, while 1 corresponds to strong dependence [139-140]. Including information from neighboring ZIP codes to further inform the estimate for each ZIP code, even when the sample size is small, has been demonstrated to create sufficient statistical power to generate unbiased estimates [141]. This is achieved by assuming a proper CAR prior, defined as $N(s_{j|k}, 1/\tau_s m_j)$, where $s_{i|j}$ is the pooled mean of area j, based on the adjacent areas k, and m_j are the number of ZIP codes neighboring j, while τ_s is the precision that controls the amount of smoothing [142-143]. By convention, the intercept and regression coefficients were assigned a conservative normal prior with a mean of 0 and a standard deviation of 0.00001. Estimation of the model parameters was carried out with MCMC simulation techniques

that were implemented in R version 3.0.1 (R Development Core Team, 2014). Model convergence was monitored using a Monte Carlo standard error threshold of 0.1 [144]. For this analysis, a total of 1,000,000 posterior samples were generated.

All statistical models were adjusted for *a priori* factors potentially associated with HPV vaccine uptake, including sex, age (mean-centered), race (white, African American, American Indian/Alaska native, Asian, or other), ethnicity (Hispanic vs. non-Hispanic), educational attainment (some high school, high school graduate, some college or technical school, college graduate, or graduate school), sexual orientation (heterosexual, homosexual/gay/lesbian, or bisexual), and political views (very conservative, conservative, moderate, liberal, or very liberal). Initially, the model was fit maintaining all the variables. The final model retained all covariates that were statistically significant. Results for regression coefficients are presented, along with odds ratios and the associated 95% credible intervals. The random effect terms can be interpreted as the effect of ZIP code on HPV vaccination uptake for each individual.

4.5 Results

Characteristics of the study sample are presented in Table 4.1. In all, 46.2% of participants had received at least one dose of HPV vaccine, with 67.7% of women reporting having been vaccinated compared to 13.0% of men. Of those who initiated the vaccine series, 71.1% completed the entire three-dose series (79.6% of women and 26.3% of men). Participants who had been vaccinated against HPV (i.e. received ≥1 dose of the vaccine) were younger (of those over age 25, 30.1% were vaccinated compared to 69.9% who were not). Vaccine receipt was lower among those who identified themselves as

politically "conservative" or "very conservative" as opposed to politically "liberal" (24.6% compared to 53.3%).

HPV vaccination was found to exhibit strong spatial dependence ($\hat{\rho} = 0.9966$). The average spatially dependent random effect estimate for each ZIP code is shown in Figure 4.1. The magnitude of these effects is represented with varying shades of blue, with larger effects shown with darker shades of blue. The CAR model also successfully converged, as the maximum Monte Carlo standard error was 0.035 (which was below our threshold of 0.1), indicating that a sufficient number of posterior samples were generated for the estimates to stabilize. Estimates for the best-fitting CAR model are shown in Tables 4.2 and 4.3. After accounting for spatial dependence using the CAR model, age, sex, and political preferences remained significant predictors of HPV vaccine receipt. Specifically, older age (OR = 0.77 per year, 95% CI = 0.72-0.83) and being male (OR=0.03, 95% CI = 0.02-0.06) were associated with a decreased odds of HPV vaccine receipt. Moderate and liberal political preferences (referent to very conservative and conservative preferences) were associated with an increased odds of HPV vaccine receipt (moderate OR = 3.24, 95% CI = 1.62-6.49; liberal OR = 5.32, 95% CI = 2.68-10.58). For comparison, regression coefficients, odds ratios, and corresponding 95% confidence intervals from a traditional logistic regression model that does not account for spatial dependence were also estimated and are also presented in Tables 4.2 and 4.3. Compared to the traditional logistic model, estimates from the CAR model were greater in magnitude for all covariates. Of note, in the traditional logistic regression model,

education and race were statistically significant factors but were not significant in the CAR model.

4.6 Discussion

In this study, HPV vaccination was found to exhibit strong spatial dependence, indicating that spatial statistical models are needed to accurately identify and estimate factors associated with HPV vaccine uptake. As a result, ignoring this spatial dependence can lead to biased point estimates and overly narrow credible intervals. Consistent with other studies, younger age, female gender, and political views were found to be significant predictors of HPV vaccination (after accounting for spatial dependence) [97-99, 135]. The associations of age and sex with HPV vaccine receipt can be attributed, in part, to the evolving ACIP recommendations, as they were first recommended for use in young girls and were later expanded to include young boys. Conservative political views have also been found to be associated with decreased knowledge of HPV, lower perceived risk of infection with HPV, and stronger views against premarital sex [145].

However, contrary to other studies that have not accounted for spatial dependence, this study found that education and race were not significant predictors of HPV vaccination [97-99, 135, 146-147]. Racial disparities (and other disparities) have been shown to be pronounced in some areas, while less evident (or absent) in other areas [148-150]. Although the existence of these disparities is well documented, the overall average effects can mask variation across local areas [151]. For example, in a traditional regression analysis when minority girls live in regions with systematically different rates

of HPV vaccine uptake, and the region is not controlled for, one could erroneously conclude that racial "disparities" exist when in fact the where people live is the significant predictor of vaccination. Thus, ignoring geography (i.e. the spatial dependence of the data) may lead to incorrect inference. Previous studies that have attempted to describe geographic variation in HPV vaccine uptake have either ignored spatial dependence completely or have not correctly accounted for it using spatial statistical models. Therefore, these studies have concluded that covariates such as education and race were significant predictors of receipt of the HPV vaccine when these conclusions are likely to be biased because they do not account for spatial dependence. Using models that can account for spatial dependence is requisite in order to identify independent predictors that are truly associated with HPV vaccination (as opposed to spatially confounded covariates), particularly when analyzing data from varying geographic locations.

This study demonstrates the geographical variation of HPV vaccination within ZIP codes in the Twin Cities Metropolitan Area (at a scale that is smaller than that which is currently available through national surveys) and emphasizes the advantage of estimating vaccine uptake at local levels (i.e. intra-state or intra-county). Previous studies have demonstrated that HPV vaccination uptake varies across large geographical regions and within state boundaries [100-101, 133, 135]. HPV vaccine policies, availability, costs, financial assistance, and education materials have been shown to vary widely across states or within more defined geographic regions [122]. As a result, variation at state and national levels may not reflect the variation in HPV vaccine uptake

occurring at a local level. A finer level of analysis was not possible in these studies because of the sparseness of data at the county and ZIP code levels, which is in part attributable to national surveys aggregating or suppressing responses due to participant identification concerns. One strength of this study is that ZIP code level data were available to conduct a more detailed spatial analysis. Specifically, this study demonstrates that HPV vaccine uptake does indeed vary widely within counties at the ZIP code level. This study also identifies significant predictors of vaccination after accounting for spatial autocorrelation, and isolates ZIP codes where targeted efforts are needed and may eventually have the greatest impact on reducing the HPV-associated disease burden in the Twin Cities.

There are several limitations to this study. First, all study measures were self-reported by persons over the Internet and may be subject to under or over-reporting. However, recent studies have shown recall of HPV vaccination status to be accurate [152]. In addition, Internet-based studies have shown increased self-disclosure and reporting with online surveys, which may reduce potential response biases (e.g. interviewer bias or social desirability) [105, 107]. Second, the spatial analysis was conducted at the ZIP code level and assumes a common ZIP code level effect, so within-ZIP code differences may be masked. However, to our knowledge, this study has examined HPV vaccination at the smallest unit thus far. In addition, this study utilizes cross-sectional data and temporal effects cannot be established.

In conclusion, the results from this study demonstrate that more detailed and local assessments of HPV vaccine uptake that account for spatial dependence are necessary as

ZIP code level patterns differ significantly from aggregated state and national patterns. Future work is needed to further pinpoint areas with the greatest disparities and how to then access these populations to improve vaccine uptake.

Table 4.1. Characteristics of study participants by HPV vaccination status.

	Vaccinated (n=351)		Not Vaccinated (n=409)		Total (n=760)	
	N	%	N	%	N	%
Age, in years						
18-20	86	51.8	80	48.2	166	21.8
21-25	209	51.2	199	48.8	408	53.7
26-30	56	30.1	130	69.9	186	24.5
Gender						
Female	312	67.7	149	32.3	461	60.7
Male	39	13.0	260	87.0	299	39.3
Race						
White	298	46.3	346	53.7	644	84.7
Black	22	61.1	14	38.9	36	4.7
Am. Indian/AL native	4	50.0	4	50.0	8	1.1
Asian	15	34.1	29	65.9	44	5.8
Other	12	42.9	16	57.1	28	3.7
Hispanic/Latino						
Yes	13	48.1	14	51.9	27	3.6
No	336	46.2	391	53.8	727	96.4
Education						
Some High School	4	1.1	3	0.7	7	0.9
High School Graduate	19	5.4	25	6.1	44	5.8
Some College or Tech. School	135	38.5	151	36.9	286	37.6
College Graduate	152	43.3	175	42.8	327	43.0
Graduate School	41	11.7	55	13.4	96	12.6
Sexual Orientation						
Heterosexual	311	45.7	370	54.3	681	89.7
Homosexual, gay, or lesbian	12	36.4	21	63.6	33	4.3
Bisexual	21	65.6	11	34.4	32	4.2
Don't know/Refused	7	53.8	6	46.2	13	1.7
Political Views						
Very Conservative	1	4.5	21	95.5	22	2.9
Conservative	28	29.2	68	70.8	96	12.6
Moderate	103	44.6	128	55.4	231	30.4
Liberal	154	52.0	142	48.0	296	38.9
Very Liberal	65	56.5	50	43.5	115	15.1

HPV indicates human papillomavirus

[a]Other indicates Native Hawaiian or Pacific Islander, more than one race, or a response of "other."

Table 4.2. Regression estimates for factors associated with HPV vaccination from traditional logistic regression and spatial CAR models.

	Traditional Logistic Model		**Spatial CAR Model**	
	Estimate	Standard Error	Estimate	Standard Error
Intercept	-0.132	0.253	-0.702	0.329
Age[a]	-0.139	0.029	-0.273	0.036
Male[b]	-2.629	0.205	-3.560	0.239
Political Views[c]				
Moderate	0.850	0.295	1.176	0.355
Liberal	1.036	0.285	1.672	0.351
Very Liberal	1.233	0.336	1.755	0.399

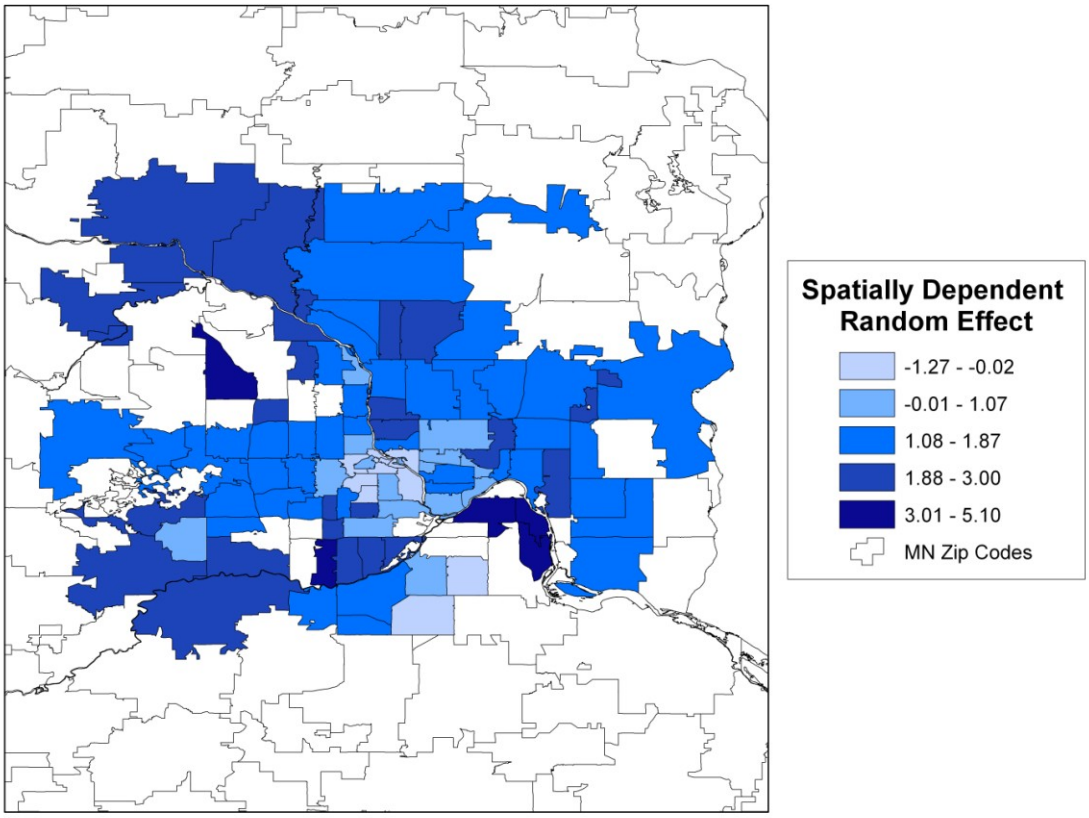
HPV indicates human papillomavirus
[a]Age is centered at 23.24 years old
[b]Referent to females
[c]Referent to combined responses of "very conservative" and "conservative"

Table 4.3. Odds ratio estimates for factors associated with HPV vaccination from traditional logistic regression and spatial CAR models.

	Traditional Logistic Model		**Spatial CAR Model**	
	Odds Ratio	95% CI[a]	Odds Ratio	95% CI[b]
Age[c]	0.87	(0.82-0.92)	0.76	(0.71-0.82)
Sex				
Female	1.0	(referent)	1.0	(referent)
Male	0.07	(0.05-0.11)	0.03	(0.02-0.05)
Political Views				
Conservative[d]	1.0	(referent)	1.0	(referent)
Moderate	2.34	(1.31-4.17)	3.24	(1.62-6.49)
Liberal	2.82	(1.61-4.92)	5.32	(2.68-10.58)
Very Liberal	3.43	(1.78-6.63)	5.78	(2.64-12.65)

HPV indicates human papillomavirus
[a]95% Confidence Interval
[b]95% Credible Interval
[c]Age is centered at 23.24 years old
[d]Referent group consists of "conservative" and "very conservative" responses

Figure 4.1. Map of spatially dependent random effect estimates from the final spatial CAR model.



The average spatially dependent random effect estimate was mapped for each ZIP code in the study area. The magnitude of these effects is represented with varying shades of blue, with larger effects shown with darker shades of blue.

Chapter 5. Manuscript 3: Human papillomavirus infection in women who submit self-collected vaginal swabs after internet recruitment

5.1 Overview of Manuscript 3

The objective of Manuscript 3 was to determine the feasibility of obtaining self-collected HPV test-based screening from women recruited via the Internet. This project aimed to determine whether women who were recruited via the Internet would provide self-collected biological samples for cervical cancer screening (HPV DNA testing) and if this screening method was an acceptable alternative to clinic-based screening (Aim 4). This at-home self-collection approach may also reduce health disparities by offering an approach that might be more acceptable to women from different backgrounds, including those who may refuse screening due to cultural issues, inconvenience, or cost.

5.2 Summary

Background: Submission of vaginal samples collected at home could remove barriers that women face in getting screened for cervical cancer.

Methods: From December 2013 to January 2014, women aged 21-30 years were recruited online to participate in either (1) self-collected testing for human papillomavirus infection (HPV) and an online survey, or (2) an online survey regarding their perceptions of self-collected testing for HPV infection. Demographics, risk factors, testing perceptions, and satisfaction with self-collected testing were assessed with online questionnaires. Women who performed self-collection were sent a home sampling kit by U.S. mail, which was returned via U.S. mail for HPV testing.

Results: A total of 197 women were enrolled, with 130 completing the online survey and 67 participating in self-collection. Of the 67 women who were sent kits, 62 (92.5%) were returned for testing. Sixty kits contained a sample sufficient for testing. The overall prevalence of HPV infection was 17.8%, yet 6 women (9.7%) were infected with >1 type of HPV. Women who self-collected a sample reported more favorable attributes of self-collection compared to women who only participated in the online survey, including ease of sampling (87.1% vs. 18.9%), no pain during sampling (72.6% vs. 5.6%), and lack of embarrassment (67.7% vs. 12.9%).

Conclusions: A high prevalence of HPV infection was demonstrated among women recruited via the internet. Online recruitment and at home screening methods have the potential to engage women in screening by offering an approach that might be more acceptable to women of different backgrounds.

5.3 Introduction

Persistent infection with human papillomavirus (HPV) is the major cause for cervical cancer and genital warts [11, 153]. Genital HPV is sexually transmitted, and infections are very common, with the prevalence of HPV infections peaking between ages 18 and 30 [60-61, 154]. Most women in the world will be infected with genital HPV(s) at some time in their lives, with a lifetime risk of infection between 50-80% [49]. Most infections will clear spontaneously, however an estimated 10-20% of infections can persist, progress to precancerous lesions and eventually invasive cancer of the cervix if left untreated [2, 155-156].

HPV DNA testing is currently recommended in combination with cervical cytology for cervical cancer screening in women 30 years and older[157] due to its high sensitivity for detecting cervical precursor lesions [158]. Recently, the Food and Drug Administration approved the use of primary stand-alone type specific HPV DNA testing in women aged 25 years or older [159]. Currently, HPV DNA testing is typically performed in a clinic by a clinician who collects a cervical sample during a pelvic exam [160]. However, HPV DNA has the potential, unlike cervical cytology, to be self-collected. Studies of self-collected vaginal samples for HPV testing, which can be collected in non-clinical settings, have shown a high concordance between samples collected by patients and those obtained by clinicians [93, 161-164]. In addition, women have generally responded positively to collecting their own samples [94, 165-167]. However, these studies have been conducted in clinical settings in which clinic staff has usually provided instructions for self-collection. It is unclear whether HPV tests can be collected independently of a clinic setting and clinician instructions.

One potentially promising method for accessing women who are eligible for cervical cancer screening is internet-based recruitment via social networking sites such as Facebook™. Social media advertising permits the advertiser to target messages to specific groups based on their characteristics (i.e. age or race) and geographic location. One survey conducted in the U.S. in 2013 estimated that 90% of young adults aged 18-29 have a Facebook account, with 71% identifying Facebook as their primary social media site [119]. To date, no HPV self-collection study has used online recruitment to recruit women to self-collect a sample for HPV testing [89, 167-170]. The objective of this

study was to determine the feasibility of initiating at-home HPV self-collected testing among women aged 21 to 30 in Minnesota who had been recruited using advertisements on the social networking site Facebook.

5.4 Methods

Study Participants

This study is based on the Survey of Minnesotans About Screening and HPV (SMASH) study, which is a cross-sectional study of English-speaking men and women aged 18-30 years from the Twin Cities Metropolitan Area of Minnesota (Manuscript 1). Briefly, we utilized targeted advertising on Facebook from November 2012 to January 2013 to promote our study to men and women who met the study eligibility criteria (as specified in their user profiles). Men and women who clicked on a study advertisement were redirected to the secured SMASH study website, where they were invited to participate in an online survey. After providing consent, participants were asked to answer questions regarding HPV vaccination, cancer screening, and barriers/intentions of receiving these health services. Participants were also asked if they would like to be contacted for future health studies about HPV. In total, 369 (out of 557) female participants responded in the SMASH survey that they would be willing to participate in future HPV studies. To be eligible for the present study, participants had to be female, aged 21 to 30 years, not pregnant, not immunocompromised, could not have received treatments in the preceding 2 years for cervical lesions, and must have resided in the greater Twin Cities Metropolitan Area. Of the 369 women who expressed their interest in future HPV studies, 300 met the eligibility requirements for this study. This study was

approved by the University of Minnesota Institutional Review Board, Minneapolis, Minnesota.

Participant Selection and Assignment

Participants were assigned to either (1) self-collect a sample and complete an online survey regarding their experiences or (2) complete an online acceptability survey regarding their perceptions of self-collected testing for HPV infection (see Figure 1). A random sample of eligible women (n=123) were invited to participate in at-home self-collected HPV DNA testing and to complete an online survey. The remaining women who were not invited to self-collection (n=177) and those women who were invited to participate in self-collection but did not enroll in self-collection (n=56) were invited to complete the online acceptability survey. Potential participants were contacted up to three times by email and invited to participate. Each email contained a secured link to the study website where participants could learn more about the study and choose to participate. Women that responded to the email invitations and provided informed consent were enrolled in the study.

Self-Collection Arm

Women who were invited to participate in the self-collection arm of the study were asked to 1) provide a personal mailing address, 2) to self-collect a vaginal sample at home for HPV DNA testing, 3) to return the sample via mail, and 4) to complete an acceptability questionnaire after self-collection (this will be referred to as the post-collection survey). Women that completed the sampling, returned the sample, and completed the post-collection survey were issued a $50 electronic gift card as compensation.

Self-Collection Kit

Self-collection kits were mailed to all participants in the self-collection arm of the study. The self-collection kit contained illustrated instructions for collecting a vaginal sample, disposable examination gloves, two Q-tip swabs for sampling, a plastic vial to protect the samples during shipping, and a pre-paid envelope for return mailing. Women were instructed to wash their hands, gently insert the Q-tip into their vagina as far as they could without hurting (as they would a tampon), rotate the Q-tip three times while inside their vagina, remove the Q-tip, and insert the Q-tip directly into a plastic vial for transport. Once the samples were collected, participants were asked to indicate the date the sample was collected and to package the samples for safe shipping. They were then instructed to place the samples in a mailbox (or deliver to a nearby U.S. post office) on the same day that they collected the samples.

Post Self-Collection Survey

Women who completed self-collection were asked to complete a questionnaire about their experiences with the self-collection process. Specifically, participants were asked to report any pain or discomfort they experienced while using the kit (using 10-point Likert scales), what they liked and disliked about the self-collection process, whether they preferred self-collected screening or clinician-based screening, how comfortable they would feel if they were to receive a negative HPV test result from this kind of testing, and their preferred method of notification if they were to be informed of a positive HPV test result. The survey was administered using the online survey assessment tool SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA).

Acceptability Survey Arm

Women who were assigned to the online acceptability survey arm of the study were invited to complete a short online survey (administered using Survey Monkey) immediately after providing informed consent. The survey contained questions regarding preferences, opinions, and perceptions of self-collecting a vaginal sample for cervical cancer screening. The questions were the same as the post-collection survey questions, except that they asked participants how they would feel under the hypothetical scenario of self-collecting a sample without actually having participated in self-collected screening. Participants who completed this survey received a $5 electronic gift card as compensation.

Measurements

In order to determine the feasibility of recruiting women via the Internet to participate in HPV DNA testing, the mean time for a subject to return a kit, the number of kits that were successfully completed, and the overall response rate of women were tabulated. Mean response time was measured as the number of days that elapsed between sending the kit until the sample was received at the study laboratory. The overall response rate was calculated by counting the number of women who responded to the study email invitations divided by those who were contacted and invited to participate.

The number of successful kits was measured as the number of returned samples that contained a sufficient sample (yes/no) to conduct HPV DNA testing. Each sample was tested for the presence of HPV DNA using PCR [171]. Samples that were positive for HPV were genotyped using restriction fragment polymorphism analysis. This method discriminates between infections with single, multiple and novel HPV types. Samples

that did not contain enough cellular matter for HPV DNA testing were classified as insufficient for testing.

5.5 Results

Self-Collection Arm

Of 123 women who were invited to participate in self-collection, 67 (54.5%) agreed to provide a self-collected vaginal sample for HPV testing. Of the 67 kits that were mailed to these women, 62 (92.5%) were returned for HPV testing. Sixty kits contained a sample sufficient for testing; 2 kits did not. Of the samples that were sufficient for testing, 17.8% (11 out of 60) were positive for at least one type of HPV. Six samples (9.7%) were positive for >1 HPV type. The overall mean time for a subject to return a kit was 13.1 days (SD = 13.6). Participant characteristics are presented in Table 5.1. Women who enrolled in the study were also similar to those who did not enroll in terms of age, race, education, and HPV vaccination status, irrespective of their assignment to self-collection or to the acceptability survey (see Tables 5.2 and 5.3).

Women who self-collected a vaginal sample at home reported that they liked the self-collection process because it was "easy" (87.1%), "not painful" (72.6%), and "private" (85.5%). Women reported that their primary dislike of the self-collection process was that they were "not sure they did it right" (56.5%), or because "it was painful" (8.1%). In all, two women (3.2%) reported that they did not like self-collecting a sample at home. After performing a self-collected HPV test, 1 out of 4 women preferred this method to a pelvic exam and Pap smear by a clinician, with 1 in 3 women preferring self-collection in combination with a pelvic exam and Pap smear by a clinician. Under

the hypothetical scenario of receiving a negative HPV test result after submitting a self-collected sample, 25.8% of women reported that they would feel comfortable not seeing a physician, compared to 30.6% of women who would not feel comfortable and 40.3% who might feel comfortable not seeing a physician (see Table 5.4).

Acceptability Survey Arm

Of the 233 women invited to participate in the online acceptability survey, 130 (55.8%) completed the survey. These women reported that they would like the self-collection process because it would be "private" (23.7%), "could be done by myself" (22.0%), and because it would be "easy" (18.9%) (refer to Table 5.4). The main reasons that women reported that they would not like the self-collection process is because they would "not be sure they did it right" (66.5%) and that it would be "painful" (20.8%). Ten women (2.5%) reported that they did not like the idea of self-collecting a sample at home. Twenty-eight percent of women reported that they would prefer to collect a sample at home next time they needed to be screened, compared to 40.5% who would prefer to have a routine pelvic exam and Pap smear performed by a clinician. Under the hypothetical scenario of receiving a negative HPV test result after submitting a self-collected sample, 25.4% of women reported that they would feel comfortable not seeing a doctor, compared to 19.2% of women who would not, with 47.7% reporting "maybe."

5.6 Discussion

Using Facebook as a recruitment tool to invite women to participate in at-home self-collected HPV testing showed promising results. More than half (54.5%) of women who were invited to self-collect a vaginal sample for HPV testing participated in this

study, and 92.5% of these women successfully completed and returned a sample for testing. A high prevalence (17.8%) of HPV was detected using self-collection, which is comparable to studies of self-collection that have been conducted in controlled healthcare settings (18.4%) and to that of community-based screening in rural settings (17.6%) providing further evidence of the performance of self-collected sampling in non-clinical settings [163, 172]. The vast majority (87.1%) of women who completed the kit found self-collection to be easy to do. These results indicate that women who are recruited on the Internet can and will participate in HPV screening outside of traditional healthcare settings. If HPV vaccination uptake continues to increase among young women, this at-home screening method may provide an alternative, cost-effective method for screening in an era with an extremely low incidence of cervical cancer.

Women who self-collected a vaginal sample reported more favorable attributes of self-collection compared to women who only participated in the online survey, such as ease of sampling (87.1% vs. 18.9%), no pain during sampling (72.6% vs. 5.6%), and lack of embarrassment (67.7% vs. 12.9%). These findings are consistent with studies of self-collected samples for *Chlamydia trachomatis* screening which have shown that home testing is a strong facilitating factor for participating in testing and a more acceptable method than clinician-collected samples among young women [173-174]. This finding is encouraging, as it demonstrates that self-collection is not only acceptable to women, but also a viable solution to collect a sample without invoking the time and cost of visiting a healthcare professional. However, it is important to note that women would likely benefit if they were to receive an introduction to self-collection methods within a clinical

setting and then proceed to use self-collection methods at the next recommended screening interval. This subsequent screening "visit" could then be managed with ease using online reminders and strategies to complete home self-collection at the appropriate time.

Recruiting women via the Internet is highly cost-effective and time efficient. Of the women who participated in self-collected HPV testing, 37.5% responded to the first study invitation and requested a kit within 48 hours of receiving the invitation. As was previously shown, the average advertising cost to recruit a person via Facebook was $1.36 (Manuscript 1). This approach to data collection may also be particularly well suited to surveillance studies that wish to identify risk factors associated with sensitive topics as other studies have shown that internet surveys can elicit responses on sensitive topics and also avoid bias associated with in-person interviews [105, 107].

One limitation of this pilot study is that subjects were recruited from a previous study and represent a small convenience sample of women in the Twin Cities Metropolitan Area. Thus, the women who participated in the acceptability survey or who returned a self-collection kit may not be representative of the general population. However, the objective of this study was to determine if the study protocol and procedures (i.e. internet recruitment) were acceptable to women and if they could be applied to more generalized populations to increase cervical cancer screening.

Another limitation of this study is that self-collected HPV tests are not approved for use in any age group. Further, HPV DNA testing in women younger than 30 years old is not recommended in clinical practice although the cobas HPV test (Roche

Molecular Systems, Incorporated, Pleasanton, California) just recently received FDA approval for use in women aged 25 years and older [159]. Thus, the acceptability of HPV DNA testing in this younger, more technologically proficient population may not translate to populations of women who are currently in their late 30s and early 40s for whom HPV DNA testing (in conjunction with cervical cytology) is a recommended screening practice for cervical cancer prevention. However, the guidelines for cervical cancer screening have evolved quickly as new technologies have emerged and make it plausible that self-collected HPV DNA testing may be used in the future to detect and monitor HPV infections in high-risk young women who do not participate in traditional screening and among this population of women as they age. In addition, it has been estimated that screening with HPV DNA testing followed by cytology in younger women who have been vaccinated against HPV to be more cost-effective than the current screening practices [175]. Therefore, accessing these younger populations for screening using HPV DNA testing may not only prevent disease, but it may also result in lower costs and increased cervical cancer screening.

In conclusion, the results from this study suggest that recruiting young adults via the Internet to participate in HPV testing is highly efficient and cost-effective. In addition, self-collected screening was found to be acceptable and favorable among women aged 21 to 30 years. Collectively, these findings suggest that this recruitment and screening approach may be used to facilitate targeted screening among high-risk sub-populations, including under-screened and underprivileged women, to reduce the burden of HPV disease. Future work is needed to examine how at-home testing can be used in

conjunction with traditional screening practices to optimize screening intervals and reduce unnecessary healthcare costs.

Figure 5.1. Manuscript 3 study flowchart.

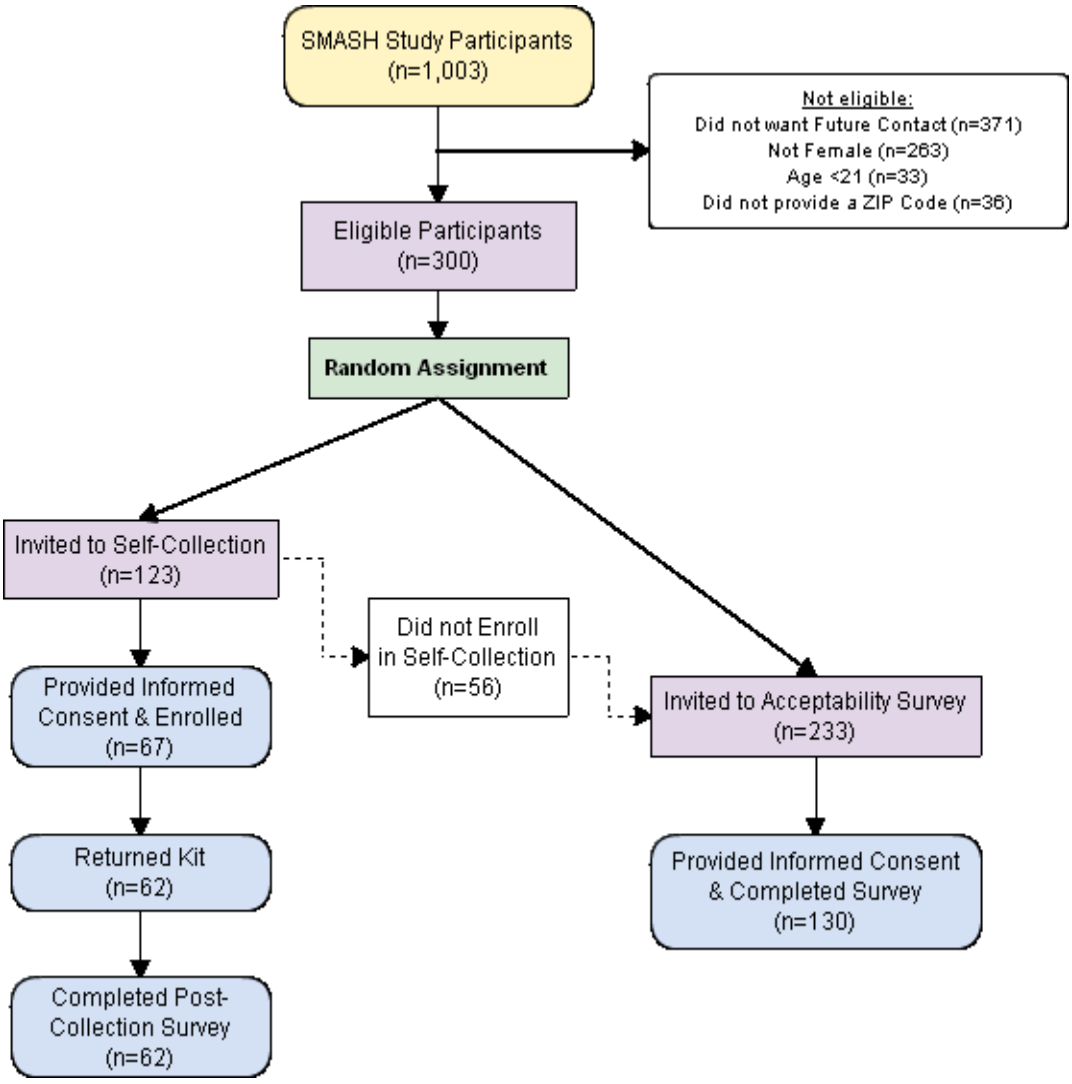


Table 5.1. Selected characteristics of study participants.

	Self-Collection Arm (n=62)		Acceptability Survey Arm (n=130)	
	N	%	N	%
Age, in years				
20-22	19	22.0	42	32.1
23-24	17	19.7	45	34.4
25-27	15	17.4	22	16.8
28-30	11	12.7	22	16.8
Mean age	24.4	2.6 (SD)	24	2.7 (SD)
Race				
White	54	87.1	103	78.6
Black	3	4.8	8	6.1
Asian	1	1.6	8	6.1
Am. Indian/AL native	3	4.8	4	3.1
Other	1	1.6	8	6.1
Education				
Some High School	0	0.0	1	0.8
High School Graduate	2	3.2	7	5.4
Some College or Tech. School	11	17.7	41	31.5
College Graduate	41	66.1	62	47.7
Graduate School	8	12.9	19	14.6
Sexual Orientation				
Heterosexual	55	88.7	119	90.8
Homosexual, gay, or lesbian	2	3.2	2	1.5
Bisexual	4	6.5	8	6.1
Choose not to answer	1	1.6	2	1.5
Ever had HPV vaccine				
Yes	43	69.4	90	70.9
No	18	29.0	35	27.6
Don’t know	1	1.6	2	1.6
Income				
Under $15,000	16	27.1	33	25.4
$15,000 to $24,999	5	8.5	17	13.1
$25,000 to $34,999	9	15.3	14	10.8
$35,000 to $49,999	9	15.3	19	14.6
$50,000 to $74,999	10	16.9	18	13.8
$75,000 to $99,999	4	6.8	6	4.6
More than $100,000	6	10.2	11	8.5
Prefer not to answer	-	-	6	4.6
Don't know	-	-	6	4.6

Table 5.2. Comparison of those who enrolled in the study to participate in self-collection to those who did not enroll in the study.

	Enrolled in Self-collection (n=67)		**Did not Enroll (n=56)**	
	N	%	N	%
Age, in years				
20-22	21	31.3	19	33.9
23-24	18	26.9	22	39.3
25-27	17	25.4	7	12.5
28-30	11	16.4	8	14.3
Mean age	24.4	2.6 (SD)	23.5	2.7 (SD)
Race				
White	57	90.5	44	78.6
Black	2	3.2	4	7.1
Asian	3	4.8	4	7.1
Am. Indian/AL native	3	4.8	0	0.0
Other	1	1.6	4	7.1
Hispanic/Latino				
Yes	1	1.5	1	1.8
No	65	98.5	56	98.2
Education				
Some High School	0	0.0	0	0.0
High School Graduate	2	3.0	1	1.8
Some College or Tech. School	12	17.9	18	32.1
College Graduate	44	65.7	28	50.0
Graduate School	9	13.4	9	16.1
Vaccinated against HPV				
Yes	46	68.7	33	61.1
No	20	29.9	18	33.3
Don't know	1	1.5	3	5.6

Table 5.3. Comparison of those who enrolled in the study to participate in the acceptability survey to those who did not enroll in the study.

	Enrolled in the Acceptability Survey (n=130)		Did not Enroll (n=100)	
	N	%	N	%
Age, in years				
20-22	42	32.3	40	40.0
23-24	45	34.6	32	32.0
25-27	22	16.9	14	14.0
28-30	21	16.2	14	14.0
Mean age	24.0	2.7 (SD)	23.4	2.7 (SD)
Race				
White	103	79.2	79	79.8
Black	8	6.2	10	10.1
Asian	7	5.4	5	5.1
Am. Indian/AL native	4	3.1	0	0.0
Other	8	6.2	5	5.1
Hispanic/Latino				
Yes	2	1.6	5	5.0
No	125	98.4	95	95.0
Education				
Some High School	1	0.8	0	0.0
High School Graduate	7	5.4	4	4.0
Some College or Tech. School	41	31.5	40	40.0
College Graduate	62	47.7	43	43.0
Graduate School	18	13.8	13	13.0
Vaccinated against HPV				
Yes	89	70.6	63	63.6
No	35	27.8	35	35.4
Don't know	2	1.6	1	1.0

Table 5.4. Acceptability and trust of self-collected HPV DNA screening by study arm.

	Self-Collection Arm (n=62)		Acceptability Survey Arm (n=130)	
	N	%	N	%
Likes				
It was easy	54	87.1	75	18.9
It was not painful	45	72.6	22	5.6
I could do it by myself	52	83.9	87	22.0
It was private	53	85.5	94	23.7
It was not embarrassing	42	67.7	51	12.9
I didn't have to undress in front of a doctor	35	56.5	52	13.1
Nothing, I didn't like the s/c process	2	3.2	10	2.5
Dislikes				
Not sure I did it right	35	56.5	115	66.5
It was painful or physically uncomfortable	5	8.1	36	20.8
I didn't like touching myself	1	1.6	5	2.9
It was embarrassing	0	0.0	1	0.6
I felt alone	0	0.0	-	-
Nothing, I liked the s/c process	26	41.9	16	9.2
Preferred Method at next screening				
Pelvic Exam and Pap smear by doctor	15	24.2	53	40.5
Self-collect sample at home by myself	16	25.8	37	28.2
Prefer to do both	22	35.5	22	16.8
I don't like either one	1	1.6	7	5.3
I don't know	7	11.3	10	7.6
I prefer not to respond	1	1.6	1	0.8
Hypothetical situations				
Negative Result, comfortable not seeing doctor				
Yes	16	25.8	33	25.4
No	19	30.6	25	19.2
Maybe	25	40.3	62	47.7
I don't know	2	3.2	10	7.7
Positive Result, notification				
Letter	23	37.1	25	19.2
e-mail	15	24.2	47	36.2
Phone call	23	37.1	54	41.5
I don't know	1	1.6	4	3.1

Chapter 6. Conclusions and Implications for Future Research

6.1 Overview

Research describing the uptake and geographic variability in the human papillomavirus (HPV) vaccine is limited and has relied on data collected from large national surveillance programs. The overarching goal of this dissertation was to estimate the uptake of the HPV vaccine at the ZIP code level and to determine if uptake varied geographically. This dissertation also aimed to determine if online recruitment and at home screening methods would be acceptable to women. Each manuscript investigated a different aspect of HPV vaccination and cancer screening in the Twin Cities Metropolitan Area.

In Manuscript 1, our aims were to (1) demonstrate the feasibility and cost-effectiveness of recruiting men and women for health research through the Internet, and (2) estimate the prevalence of HPV vaccination among men and women in the Twin Cities Metropolitan Area. We recruited men and women via a targeted Facebook advertisement campaign to complete an online survey about HPV vaccination practices. Of the 2,079 men and women who responded to the Facebook advertisements and visited the study website, 1,003 (48.2%) enrolled in the study and completed the survey. The average advertising cost per completed survey was $1.36. Among those who reported their ZIP code, 881 out of 972 (90.6%) of the participants lived within the *a priori* geographically defined study area. Receipt of ≥1 dose of HPV vaccine was reported by 65.6% of women, and by 12.5% of men. This study showed that recruiting a representative sample of young men and women based on county and zip code location to

complete a survey on HPV vaccination uptake via the Internet was a cost-effective and feasible strategy. This study also highlighted the need for local estimates to assess the variation in HPV vaccine uptake, as these estimates differed considerably from those obtained using survey data that is aggregated to the state (53.8% for young women and 20.8% for young men) or national level (34.5% for women and 2.3% for men).

In Manuscript 2, our aim was to describe and evaluate the distribution of HPV vaccination uptake by ZIP code in the Twin Cities Metropolitan Area. We examined the geographic variation in HPV vaccine uptake using ZIP code level data from 760 individuals nested within 99 ZIP codes residing within a 25-mile radius of downtown Minneapolis, Minnesota. We employed proper spatial CAR models, which account for spatial dependence, in order to estimate factors associated with receipt of HPV vaccination. HPV vaccination was found to exhibit strong spatial dependence ($\hat{\rho} = 0.9967$). Accounting for spatial dependence, older age, male gender, and liberal political preference were found to be significant predictors of HPV vaccination. This study highlights the need to account for spatial dependence when looking at geographic variation in HPV vaccination. This study also underscores the need for more detailed data collected at the local level as ZIP code level patterns of HPV vaccine receipt were found to differ significantly from aggregated state and national patterns.

In Manuscript 3, our aim was to obtain self-collected vaginal samples for HPV testing from women recruited on the Internet to determine the feasibility of self-collected screening in this population. We recruited a total of 197 women, with 130 completing an online survey about self-collection and 67 participating in self-collection. Of the 67

women who were sent kits, 62 (92.5%) were returned for testing. Women who self-collected a sample reported more favorable attributes of self-collection compared to women who only participated in the online survey. A high prevalence of HPV infection was demonstrated (17.8% were infected with at least one type of HPV) among women recruited via the internet. Online recruitment and at home screening methods were shown to have the potential to engage women in screening by offering an approach that might be more acceptable to women of different backgrounds.

6.2 Significance of Findings

Results from this dissertation are important for several reasons. Results suggest that national and state surveillance programs that estimate HPV vaccine uptake do not accurately depict what occurs at a local level. This implies that recommendations and policies at these aggregate levels are also likely to overlook patterns of vaccine uptake that occur more locally and may result in continued vaccine disparities. These results also suggest that specific locations can (and should) be identified in order to maximize future intervention and vaccination strategies designed to reduce HPV-associated disease. These results also demonstrate that using the Internet is an efficient and feasible approach to collect public health data, particularly for sensitive or personal information. In addition, these results suggest that online recruitment and screening approaches may be a viable solution to facilitate targeted screening among high-risk sub-populations, including under-screened and underprivileged women, to reduce the burden of HPV disease.

6.3 Strengths and Limitations

Several strengths of this dissertation should be noted. First, this dissertation is the first to examine receipt of the HPV vaccine, cancer screening practices, and intentions/barriers to these health services within a representative study sample. Second, we collected data on HPV vaccine uptake by ZIP code, which is more detailed (i.e. higher geographical resolution) than what has been done previously in other studies. Third, this dissertation contains the first analysis to examine geographic patterns in HPV vaccine uptake while accounting for spatial dependence. Fourth, this dissertation includes the first Internet-based strategy to engage women in at-home cancer screening.

The dissertation also has several limitations. First, the cross-sectional survey design limited our ability to determine trends in vaccination and to identify causal relationships. Future research should collect data at several time points in order to address this issue. Second, all survey responses were self-reported by persons over the Internet and it is possible that survey responses were subject to under or over-reporting. However, other Internet-based studies have shown increased self-disclosure and reporting with online surveys, which may reduce potential response biases (e.g. interviewer bias or social desirability) [19, 21]. Additionally, there was no fail proof method to ensure that survey responses were unique and there remains a small probability that some participants responded more than once.

Another limitation is that the spatial analyses (Manuscript 2) were conducted at the ZIP code level and assume a common ZIP code level effect, such that within-ZIP code differences may be masked. However, ZIP codes have less variability in terms of

land area and population size than counties and states and may be more appropriate in the context of HPV vaccine uptake. Furthermore, to our knowledge, this dissertation examined HPV vaccination at the smallest areal unit thus far.

Another limitation of this dissertation is that self-collected HPV tests are not approved for use in any age group. Further, HPV DNA testing in women younger than 30 years old is not recommended in clinical practice although the cobas HPV test recently received FDA approval for use in women aged 25 years and older [159]. Thus, the acceptability of HPV DNA testing in this younger, more technologically proficient population may not translate to populations of women who are currently in their late 30s and early 40s for whom HPV DNA testing (in conjunction with cervical cytology) is a recommended screening practice for cervical cancer prevention. However, the guidelines for cervical cancer screening have evolved quickly as new technologies have emerged and make it plausible that self-collected HPV DNA testing may be used in the future to detect and monitor HPV infections in high-risk young women who do not participate in traditional screening and among this population of women as they age. In addition, it has been estimated that screening with HPV DNA testing followed by cytology in younger women who have been vaccinated against HPV to be more cost-effective than the current screening practices [175]. Therefore, accessing these younger populations for screening using HPV DNA testing may not only prevent disease, but it may also result in lower costs and increased cervical cancer screening.

Finally, results from this dissertation may not be generalizable beyond the Twin Cities Metropolitan Area. Notably, the characteristics of the SMASH study population

were similar to those of the source population. An exception however, was that our study population was more educated than the general population in the Twin Cities Metropolitan Area which may be due to the large number of colleges and universities in this area. However, it cannot be ruled out that people with lower education were less likely to access Facebook and view the advertisements although other studies have shown that lower income and less educated participants are as likely to participate in Internet-based research studies as those who with higher incomes and higher levels of education [26, 35-36].

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